Metabolic Bone Disease of Prematurity
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Mineral Accrual During Pregnancy

Calcium Accrual

- 80 percent of bone calcium contents accrued in the third trimester
- Average of 30 grams in the last trimester
- Abundant calcium binding proteins in syncytiotrophoblast

Bone Formation

Postnatal Changes: Mineral Supplies

- Maternal
  - Placental transport
- Parenteral
  - Enteral nutrition
Intestinal Calcium absorption

Intestinal Phosphate absorption

Terminology

Normal

Osteomalacia (Mineralization defect)

Osteopenia (Decreased Matrix formation)

On plain radiograph osteomalacia and osteopenia are indistinguishable

Metabolic Bone Disease of Prematurity

- Occurs up to 55% (range 30-55%) of very low birth weight infants
- Combination of both poor matrix formation (osteopenia) and mineralization defect (osteomalacia)
- Can lead to fractures

Radiograms: Full term V.S. Preterm

Metabolic Bone Disease of Prematurity

- Decreased mineralization
- Rachitic changes

Full term

Preterm (25 week) 2-week-old

Preterm (24 week) 8-week-old
Metabolic Bone Disease of Prematurity

Periosteal reaction

Preterm (24 week) 10-week-old

Preterm (25 week) 7-week-old

Etiologies

Maternal Factors
- ?? Vitamin D
- ?? Nutritional Status

Placental Factors
- Synciotrophoblast

Fetal Factors
- ?? Intrinsic bone factors
- Mineral supplies
- Intestinal absorption
- Extrauterine environment
- Chronic illnesses
- Diuretics
- Glucocorticoids

Screening for MBD

Table 1. Frequency of Tests Used to Monitor Progression/Follow-up Preliminary Screen (Total Number of Responders = 259).

<table>
<thead>
<tr>
<th>Test</th>
<th>% Responders (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphate</td>
<td>74.3 (191)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>73.9 (190)</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>70.8 (183)</td>
</tr>
<tr>
<td>X-ray</td>
<td>68.5 (179)</td>
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<tr>
<td>25-(OH)D, vitamin D</td>
<td>24.3 (62)</td>
</tr>
<tr>
<td>25-(OH)D, vitamin D</td>
<td>17.2 (47)</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>18.1 (47)</td>
</tr>
<tr>
<td>Serum magnesium</td>
<td>9.7 (25)</td>
</tr>
<tr>
<td>Urine calcium or creatinine</td>
<td>7.4 (19)</td>
</tr>
<tr>
<td>Urine phosphorus</td>
<td>1.4 (4)</td>
</tr>
<tr>
<td>Tubular phosphate reabsorption</td>
<td>1.4 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>1.4 (4)</td>
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</tbody>
</table>
Treatments

- Mineral Supplies
- Supplements (Phosphate and Calcium)
- Vitamin D
- Exercise and Physical Therapy

Vitamin D deficiency and Metabolic Bone Disease

Myth or Fact?

Vitamin D metabolism

Ergocalciferol (D2)
Cholecalciferol (D3)

25-hydroxyvitamin D (Calcidiol)

VDR

1,25-dihydroxyvitamin D (Calcitriol)

Subnormal Calcitriol level only found in:
- 1-alpha-hydroxylase def.
- Kidney failure
- FGF23 excess

Does Vitamin D deficiency contribute to MBD?

- Prevalence of Vitamin D deficiency in preterm infants: As high as 87% in LBW preterm infants at birth*
- Several studies showed that neonatal vitamin D status correlates with maternal vitamin D status**
- There are no studies that directly link Vitamin D deficiency to MBD


Vitamin D treatment

Vitamin D treatment

Original Article

Effect of different doses of vitamin D on osteocalcin and deoxypyridinoline in preterm infants

Mark M. Ketel and Ugur Elken
Department of Pediatrics, Mustafa Fatih Erol Maternity Training Hospital, Antakya, Turkey

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>300 IU/kg/day</th>
<th>400 IU/kg/day</th>
<th>500 IU/kg/day</th>
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<tbody>
<tr>
<td>Weight at birth (g), mean</td>
<td>1220</td>
<td>1155</td>
<td>1110</td>
</tr>
<tr>
<td>Gestational age (weeks), mean</td>
<td>29.7</td>
<td>29.3</td>
<td>29.6</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

- There is no difference between serum Ca, P, ALP of all groups
- Bone turnover markers (OC, DPD) are not different between all groups
Vitamin D treatment

Recommendations for preterm infants

Vitamin D Supplementation
American Academy of Pediatrics  200-400 U
ESPGHAN  800-1000 U

Vitamin D and MBD

- Individualized treatment based on the level, weight and the severity of the disease
- Higher vitamin D content in premature formula

Treatment: Mineral Supplies

Supply & Absorption  Renal & GI Loss

Treatment: Mineral Supplies


Recommendations: Enteral Feeding

Calcium  Phosphorus

- AAP\(^1\)  150-200 mg/kg/day  75-140 mg/kg/day
- ESPGHAN\(^2\)  120-140 mg/kg/day  60-90 mg/kg/day

Term V.S. Preterm Formula

Term formula  Calcium (per 100ml)  Phosphorus (per 100ml)  Vitamin D (per 100ml)
Enfamil (20 kcal)  62 mg  34 mg  60 units
Breast Milk  28 mg  15 mg  

Preterm Formula

- Enfamil Premature (24 kcal)  132 mg  66 mg  192 units
- Fortified Human Milk (24 kcal)  116 mg  64 mg  168 units

Note:
1. Abrams SA and the committee on nutrition, Pediatrics 2013;131e1676
Treatment: Phosphorus supplement

Factors that may affect phosphorus absorption

Hypophosphatemia in MBD

- Low level of NPT2b?
- Immaturity of phosphorus sensor loop?
Treatment: Calcitriol

- High PTH level can be seen in MBD due to calciopenia
- PTH promotes phosphaturia
- PTH interferes with phosphorus absorption through GI tract?
- Calcitriol can directly decrease PTH level
- Possible role of calcitriol treatment

Reduction of Parathyroid Hormone with Calcitriol in Metabolic Bone Disease of Prematurity

- 32 infants median age 91 days (min/max: 47/141) gestational age 25 weeks (23/33)
- Calcitriol starting dose: 0.05mg/kg/day (0.02/0.1) daily IV/enteral.
- PTH decreased 24 (3/259) vs. 220 (115/593) pg/ml, \( p<0.001 \)
- \( P \) increased 5.5 (2.7/7.4) vs. 4.3 (2.9/6.4) mg/dl, \( p=0.0012 \);
- TRP increased 91.5 (78/98) vs. 81.4 (59/98)%, \( p=0.04 \)
- Median time to PTH nadir was 61 days.

Stacy Rustico, MD, Andrew Charles Calabria, MD, Andrea Kelly, MD, MSCE and Heather Monk

Tactile/kinesthetic stimulation (TKS) increases tibial speed of sound and urinary osteocalcin in premature infants

- AGA infants (29-32 weeks) were randomly assigned to TKS (N=20) or Control (N=20).
- Twice daily TKS was provided 6 days per week for 2 weeks.
- TKS intervention attenuated the decrease in tibial speed of sound observed in Control infants.
- TKS infants experienced greater increases in urinary osteocalcin.
- TKS improves bone strength in premature infants by attenuating the decrease that normally follows preterm birth.

Haley S1, Beasly J, Ivaska KK, Marine H, Smith S, Moye-Milner LJ.

Improving outcome of MBD

Early Detection

Screening Criteria

- Gestation age between 24 to 30 weeks.
- Birth weight less than 1000 grams.
- Postpartum age 3 weeks.
- Received TPN for more than 2 weeks.
- Biochemical findings: Serum phosphorus less than 5 mg/dL
  - Serum Alk Phosphatase more than 500 u/L.
- Repeated diuretics use.
- Prolonged course of glucocorticoid use.
- Radiographic evidence of decreased bone mineral content.
Treatments

- Adequate mineral supplies
  - Fortified formula: Premature formula
  - Phosphorus supplement:
    - Neutral Phos K, Liquid potassium phosphate
- Calcitriol (hyperparathyroidism)

Future Studies

- Factors affecting phosphorus homeostasis
  - Intestinal phosphorus absorption
  - Renal phosphorus reabsorption
- Improving intestinal phosphorus absorption

Tender Love & Care