Mineral metabolism in Preterm infants on Parenteral and Enteral Nutrition

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Assessment of bone growth and mineralisation during the fetal life
3a-Physiological changes

Factors influencing bone growth and mineralisation during the fetal life

- Adequate protein supply.
- High Ca and P supplies.
- Hormonal environment: maternal Vit D status, low PTH, high oestrogen.
- Physical activity.
- Genes

- In utero, modeling is largely predominant to remodeling. Remodeling process is suppressed during the fetal life in relation to the relative fetal hypercalcemia and the suppression of the PTH secretion.
Ca, P and Vit D requirements, for preterm infants

Introduction

Fetal retention

Metabolic balances

Bone mineralisation

Conclusion

**Fetal Ca accretion measurements with carcass analysis, neutron activation and DEXA**

For DEXA, Ca content was calculated as $Ca = 0.456 \times BMC + 1.56$

<table>
<thead>
<tr>
<th></th>
<th>Fetal accretion (mg/kg*d)</th>
<th>Human milk supply (mg/kg*d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>Magnesium</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Ca, P and Vit D requirements for preterm infants

**Fetal retention**

**Metabolic balances**

**Bone mineralisation**

**Conclusion**

**Fetal Vit D status**

Mothers: n=92

Cord blood: n=96

**Mother to infant relationship**

C Pieltain & J Rigo 2008
Fetal Ca Accretion

Transplacental flux

In utero

Plasma Pool

Bone growth and modeling

Reference values of vBMD according to gestational age in preterm and term infants at birth

\[ y = 0.194 \times \text{GA} + 3.89; \text{SD}=0.86; n=106; r=0.617 \]
Post-natal Mineral Requirements
Postnatal changes in bone growth and mineralisation

- Limited mineral supply due to GI absorption (oral) or Ca solubility (parenteral).
- Predominant influence of bone strength and tissue strain.
- Postnatal Vit D status and PTH surge.
- Remodeling process in bone metabolism increasing bone turnover.
Ca, P and Vit D requirements for preterm infants

Calcium, intact parathyroid hormone [PTH(1-84)], carboxy terminal PTH (cPTH), and vitamin D binding protein (DBP) concentrations in cord serum and at days 1, 2, 5, 10, and 30 after birth in 15 preterm infants

<table>
<thead>
<tr>
<th></th>
<th>Calcium</th>
<th>PTH(1-84)</th>
<th>cPTH</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/L</td>
<td>pmol/L</td>
<td>pmol/L</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Cord serum</td>
<td>2.24 ± 0.09</td>
<td>11 ± 3</td>
<td>48 ± 8</td>
<td>4.43 ± 0.37</td>
</tr>
<tr>
<td>Day 1</td>
<td>1.94 ± 0.04&lt;sup&gt;2&lt;/sup&gt;</td>
<td>66 ± 11&lt;sup&gt;2&lt;/sup&gt;</td>
<td>125 ± 15&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.40 ± 0.34</td>
</tr>
<tr>
<td>Day 2</td>
<td>1.85 ± 0.05&lt;sup&gt;2&lt;/sup&gt;</td>
<td>87 ± 11&lt;sup&gt;2&lt;/sup&gt;</td>
<td>168 ± 5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.96 ± 0.23</td>
</tr>
<tr>
<td>Day 5</td>
<td>2.22 ± 0.05</td>
<td>67 ± 9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>152 ± 16&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6.21 ± 0.26&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day 10</td>
<td>2.45 ± 0.06</td>
<td>23 ± 4</td>
<td>69 ± 6</td>
<td>6.03 ± 0.30&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day 30</td>
<td>2.44 ± 0.05</td>
<td>38 ± 7</td>
<td>80 ± 11</td>
<td>5.16 ± 0.23</td>
</tr>
</tbody>
</table>

<sup>1</sup> ± SEM. The infants’ mean birth weight was 1578 ± 78 g and their mean gestational age was 31.7 ± 0.5 wk. Serum DBP was measured by a radial immunodiffusion assay (65).

<sup>2</sup>Significantly different from cord serum, *P* < 0.05 (one-factor ANOVA for repeated measures followed by Scheffe *F* test).
Introduction

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Bone mineralisation

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Normal postnatal changes in the cross section of the femoral diaphysis

F Rauch, E Schoeneau Arch Dis Child FN 2002:86;F82-85

The increase of Ca turnover could reduce the nutritional needs?
Physiological change in mineral requirements

**Postnatally**

- GI or Parenteral supply
- Plasma Pool
- 60-90 mg/kg

**Bone**
- remodeling
- growth and modeling
- vBMD = or

The increase of Ca turnover could reduce the nutritional needs?
Calcium & Phosphorus Physiology in Parenteral Nutrition

**Ca P & AA in Parenteral Nutrition**
- **Calcium**: Phosphore & AA directly available for metabolism.
- **Calcium** & Phosphorus content are limited due to their poor solubility.

**Mineralization**
As hydroxyapatite
\[ \text{[Ca}_{10}\text{(PO}_4\text{)}_{6}\text{(OH)}_2] } \]

Ca/P Ratio = 1.66 mmol/mmol = 2.15 mg/mg

**Blood Pool**

- **Calcium**: 50% Ca\(_i\) (biologically active)
  - 40% bound to protein
  - 10% complexed with org/inorg ac
  - \( \text{Régul} : \text{PTH} \uparrow, \text{vit D} \uparrow, \text{calcitonin} \downarrow \)

- **Phosphore**: 2/3 organic phosphorus
  - 1/3 inorganic phosphorus
  - \( \text{Regul} : \text{PTH} \downarrow, \text{vit D} \uparrow, \text{FGF23} \downarrow \)

**Urinary excretion**

**Phosphaturia**
Major mechanism of regulation. Related to the Renal Phosphorus load: >1.6 mmol/L
PTH \( \uparrow \), FGF23 \( \uparrow \)

**Calciuria**
Related to a relative P deficit for bone mineralization

**LBM Retention**
Around 10 mg of Phosphorus for 1 g of protein (AA) retention
Nitrogen/P Ratio = 15/1
Reference value for Phosphate serum concentration according to age

Colantonio & al
Relationship between urinary excretion of phosphorus and serum phosphate level (n=198) in preterm infants.

Hypercalciuria (>10 mg/kg*d) is related to low phosphate excretion (<3 mg/kg*d). Whereas, urinary excretion of calcium below 8 mg/kg*d is generally observed in preterm infants with a phosphorus excretion over 10-15 mg/kg*d.
Ca, P and Vit D requirements for preterm infants

**POSTNATAL CALCIUM AND PHOSPHORUS METABOLISM IN PRETERM INFANTS RELATED TO MINERAL AND VITAMIN D INTAKE**

V. Christmann & al 2013 In Press

**CA/P Molar ratio = 1.6**

Objective: to evaluate the prevalence of hypophosphatemia during the first week of life in preterm infants receiving aggressive parenteral nutrition

Method: 61 neonates below 1250 g birth weight consecutively born at Hospital Italiano de Buenos Aires hypophosphatemia was defined as a sP <4 mg dl⁻¹).

Result: hypophosphatemia was observed in 91% (CI 82-97%). The mean sP was 2.52 mg/ dl; CI 2.18-2.86 (P<0.001). Severe hypophosphatemia (<2 m/ dl) were smaller with an increase in sepsis, vasoactive drugs and mechanical ventilation.
**Composition of the parenteral solution /100ml**

- Glucose (g) 12
- AA(g) 2.7
- Na (mEq) 1.6
- K (mEq) 1.5
- Cl (mEq) 2.0
- Ca (mg) 72
- P (mg) 55
- Mg (mg) 4
- Zn (mg) 0.1
- Kcal 60

**Metabolic balances**

<table>
<thead>
<tr>
<th>(mg/kg*d)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca intake</td>
<td>100 ± 23</td>
</tr>
<tr>
<td>P intake</td>
<td>76 ± 18</td>
</tr>
<tr>
<td>Ca ur.</td>
<td>5.6 ± 4.7</td>
</tr>
<tr>
<td>P ur.</td>
<td>18 ± 14</td>
</tr>
<tr>
<td>Ca retention</td>
<td>94 ± 20 (94%)</td>
</tr>
<tr>
<td>P retention</td>
<td>58 ± 17 (76%)</td>
</tr>
</tbody>
</table>
Ca, P and Vit D requirements for preterm infants

Parenteral nutrition

Ca & P intakes:

• Ca and P supplies are necessary from the first day of life in VLBW infants on PN

• In parenteral solution, optimal molar Ca/P ratio is close to 1/1 or slightly<1

• Phosphorus need can be estimated from the AA and the Ca intakes provided by the parenteral solution:

\[
P \text{ need} = \frac{\text{Ca intake}}{2.15} + (\text{AA intake} - 1.3) \times 0.8 \times 12.3
\]
Magnesium in parenteral nutrition in VLBW infants

1. In 2013, 14 case reports of hypermagnesemia have been reported in VLBW infants on parenteral nutrition providing a maximum Mg intake of 0.55 mmol/kg*d, in the range of the recommended values. Serum magnesium levels in the 14 infants ranged from 1.025 to 1.5 mmol/l without any symptoms or serious adverse events. Kreissl A JPEN 2016

2. sMg were compared to adult reference levels (0.6 to 1.05 mmol/L) as preterm reference levels are not well defined.

3. Nevertheless the RTU parenteral solution was retrieve from the market. EMA 2013
sMg levels in VLBW infants on Parenteral nutrition

Review of sMg in VLBW infants on parenteral nutrition showed that sMg concentrations were related to Mg intake, renal immaturity (sCreatinine conc, Ibuprofen or indomethacin treatment), antenatal Mg supplementation, gestational age and postnatal age.

Rigo & al 2016 submitted
### Meta-analysis of Magnesium Concentrations in Newborns (mmol/L)

<table>
<thead>
<tr>
<th>Population, timing</th>
<th>n</th>
<th>Estimated mean and reference interval</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy newborns without magnesium supplementation during pregnancy, at birth</td>
<td>2642</td>
<td></td>
<td>0.76 (0.52, 0.99)</td>
</tr>
<tr>
<td>Healthy newborns without magnesium supplementation during pregnancy, first week</td>
<td>928</td>
<td></td>
<td>0.87 (0.50, 1.23)</td>
</tr>
<tr>
<td>Very-low-birth-weight newborns receiving parenteral solution, first week</td>
<td>393</td>
<td></td>
<td>0.97 (0.55, 1.38)</td>
</tr>
</tbody>
</table>

**Rigo & al 2016 submitted**

**Colantonio, Caliper study Clin Chem 2012**
Magnesium recommendation in PN for VLBW infants

1. Early provision of Mg is safe in Standardized PN providing a progressive intake according to volume.

2. Optimal intake range between 0.15 to 0.30 mmmol/kg*d

3. Specific reference values for preterm and neonate need to be provide by laboratories

4. sMg survey needs to be included in the biological survey of parenterally fed VLBW infants

5. Additional controls are requested in case of prenatal Mg administration, PDA treatment, transitory renal failure.
Calcium & Phosphorus Physiology during enteral nutrition in the preterm infants

**Absorption**
- Calcium: About 50-60%
- Phosphorus: About 90%

- Proximal Intestin
- Vit-D, Ionisation (low pH) ↑
- Duod., jéjunum > iléon, colon
- Less Vit-D related

**Mineralization**
- As hydroxyapatite: \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\)
- Ca/P Ratio = 2.15

**Blood Pool**
- Calcium: 50% Ca\(_i\) (biologically active)
- 40% bound to protein
- 10% complexed with en org/inorg ac

**Regul:** PTH ↑, vit D ↑, calcitonin ↓

**Phosphaturia**
- Main mechanism of regulation.
- Related to the Renal Phosphorus load: >1.6 mmol/L
- PTH ↑ FGF23 ↑

**Calciuria**
- Related to a relative P deficit for bone mineralization

**LBM Retention**
- Around 10 mg of Phosphorus for 1 g of protein retention
- Nitrogen/P Ratio = 15/1
**Calcium absorption and retention in preterm infants fed human milk without or with human milk fortifier, and preterm formulas**

<table>
<thead>
<tr>
<th></th>
<th>HM and HMF</th>
<th>Preterm formulas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CALCIUM</strong></td>
<td>n=36</td>
<td>n=22</td>
</tr>
<tr>
<td>(mg/kg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intake</td>
<td>56</td>
<td>86</td>
</tr>
<tr>
<td>Stool</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Absorption</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td>Urine</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Retention</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>Net absorption(%)</td>
<td>64</td>
<td>69</td>
</tr>
</tbody>
</table>

In human milk groups, Ca absorption and retention are related to intakes by contrast to formula groups, where it reaches rapidly a plateau due to a decrease in net absorption (%).
### Ca, P and Vit D requirements, for preterm infants

**Phosphorus absorption and retention in preterm infants fed human milk without or with human milk fortifier, and preterm formulas**

<table>
<thead>
<tr>
<th>PHOSPHORUS (mg/kg/d)</th>
<th>HM and HMF</th>
<th>Preterm formulas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=36</td>
<td>n=22</td>
</tr>
<tr>
<td>Intake</td>
<td>40</td>
<td>56</td>
</tr>
<tr>
<td>Stool</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Absorption</td>
<td>37</td>
<td>52</td>
</tr>
<tr>
<td>Urine</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Retention</td>
<td>29</td>
<td>46</td>
</tr>
<tr>
<td>Net absorption %</td>
<td>92</td>
<td>92</td>
</tr>
</tbody>
</table>

In human milk groups, P absorption and retention are related to intakes by contrast to formula groups, where absorption and retention reaches rapidly a plateau due to a decrease in net P absorption (%).
Ca, P and Vit D requirements for preterm infants

**Introduction**

Fetal retention

Metabolic balances

**Bone mineralisation**

Conclusion

*Relationship between phosphorus retention estimated from nitrogen and calcium retentions, and the results of phosphorus balances in preterm infants (n=198)*

Phosphorus retention (g/kg*day) = 0.87*estimated retention (g/kg*day) + 4.53; SD=8.1; r=0.79; p<0.00001
Enteral Nutrition

Ca & P intakes:

- Optimal Ca and P intakes is firstly related to the Ca and P absorption rate.
- Absorption rate is higher with HM than with PTF.
- With PTF absorption rate is highly influenced by heat treatment.
- In enteral nutrition, optimal molar Ca/P ratio decrease when prot/energy ratio increase.
- In PTF with a P/E ratio of 3.6g/100 kcal a Ca content of 140 mg/100 kcal, optimal Ca/P ratio is 1.6 -1.7.
Conclusions: Calcium

- Postnatal retention differs from the fetal accretion which could not be the gold standard for preterm infants.
- Postnatal acceleration of bone turnover could reduce the nutritional requirements.
- A métabolisable Calcium supply of 70 to 90 mg/kg*d is safe for pretem infants (minimal osteopenia, no fracture risk).
- Highly available Ca salts need to be use to reduce the Ca content of formulas. High mineral supplies, increasing fecal excretion, could promote hard stool, abdominal disconform and NEC in preterm infants.
- In preterm infants, the relative osteopenia followed by a catch up of mineralization is similar to pubertal mineral changes reduction of BMD at the acceleration of growth followed by relative catch up.
- Recommendations: 70 to 90 mg, 1.75 to 2.25 mmol/kg*d in Parenteral Nutrition. 120 to 140 mg, 3.0 to 3.5 mmol/kg*d in Enteral Nutrition.
Conclusions: Phosphorus

- Postnatal retention differs from the fetal accretion which could not be the gold standard for preterm infants.
- Postnatal acceleration of bone turnover could reduce the nutritional requirements.
- Phosphorus supply need to cover the Ca deposition as well as the protein deposition. A small excess is necessary to control net acid excretion.
- Highly available P salts need to be use to reduce the mineral content of formula.
- Optimal CA/P ratio for formulas can't be a fixed ratio but is related to expected Ca absorption rate and nitrogen retention (protein energy ratio).
- Plasma and urinary P need to be monitored to evaluate the adequacy of P supply.
Serum total 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25(OH)₂D] concentrations as a function of age in 15 preterm infants

Birth weight: 1578 ± 78 g; gestational age: 31.7 ± 0.5 wk; vitamin D intake 1000 IU (25 µg)/d from birth. ***,*** Significantly different from cord serum: *P < 0.05, **P < 0.01, ***P < 0.001.

Salle BL 2000
A Comparison of 3 Vitamin D Dosing Regimens in Extremely Preterm Infants: A Randomized Controlled Trial *Fort P et al J of Pediatrics 2016;174:132-8*

**Objective:** To determine the optimal dose of vitamin D supplementation to achieve biochemical vitamin D sufficiency in extremely low gestational age newborns in a masked randomized controlled trial.

**Study design:** 100 infants <28 wks GAn were randomized to placebo (n = 36), 200 IU (n = 34), and 800 IU/d (n = 30)vit D intakes. The primary outcomes were s25OHD at d28.

**Result:** s25OHD deficient (<20 ng/mL) was 67% at birth. At d28, s25OHD deficiency (<20 ng/mL) was 41% in the placebo group, 16% in the 200 IU group, and 0% in the 800 IU group (P = .2). Median s25OHD increase according to vit D intakes and PNA.

There was no evidence of biochemical or clinical over toxicity in the 800 IU group. By contrast, a trend toward fewer infants with late onset sepsis, on oxygen at 28 days or receiving steroids for BPD were observed. Suggesting the need for additional studies.
**Conclusions: Vitamin D**

- Vitamin D deficiency is frequently observed in mother during gestation and in the cord blood.
- Vitamin D status could play a significant role in fetal bone mineralization.
- Vitamin D has also several non-calcitropic functions which could be beneficial for preterm infants.
- A daily supply of 200 to 400 IU appears to be limited to restore optimal plasma concentration in preterm and late preterm infants.
- By contrast, a daily supply of 800 to 1000 IU improves the plasma concentration without adverse effects.
- Further studies are request to evaluate the vitamin D status according to intakes in ELBW infants during the first 3 months of life, and the potential role of non-calcitropic functions of Vit D in VLBW infants.
Ca, P and Vit D requirements for preterm infants

Introduction

Basis of the ESPGHAN revised recommendations for mineral requirements

1. Previous recommendations are based on fetal mineral accretion.

2. Physiological changes in bone metabolism at birth, with a stimulation of the remodeling process inducing a spontaneous reduction in bone mineral density.

3. Mineral balances show limited absorptive capability of the gastrointestinal track in preterm infants.

4. Improvement in Ca bioavailability reduce fecal Ca excretion, increase Ca retention and abolish spontaneous fracture.

5. Spontaneous early catch up of mineralization during the first months of life.
## Calcium, phosphorus et vitamin D requirements

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Ca (mg)</strong></td>
<td>/kg/j</td>
<td>/100 kcal</td>
<td>/100 kcal</td>
<td>/100 kcal</td>
</tr>
<tr>
<td>- ELBW</td>
<td>120-140</td>
<td>110-130</td>
<td>77-200</td>
<td>123-185</td>
</tr>
<tr>
<td>- VLBW</td>
<td>110-130</td>
<td>67-169</td>
<td></td>
<td>70-140</td>
</tr>
<tr>
<td><strong>P (mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ELBW</td>
<td>60-90</td>
<td>55-80</td>
<td>46-127</td>
<td>82-109</td>
</tr>
<tr>
<td>- VLBW</td>
<td></td>
<td>40-108</td>
<td></td>
<td>55-80</td>
</tr>
<tr>
<td><strong>Vit D (IU/j)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LBW(IU/100 kcal)</td>
<td>800-1000</td>
<td></td>
<td>115-364</td>
<td>100-308</td>
</tr>
<tr>
<td>- VLBW</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Considering that a calcium retention level ranging from 60 to 90 mg *kg⁻¹* *day⁻¹* ensures appropriate mineralization and decreases the risk of fracture, an intake from 120 to 140 mg *kg⁻¹* *day⁻¹* (110–130 mg/100 kcal) of highly bioavailable calcium salts and 60 to 90 mg *kg⁻¹* *day⁻¹* (55–80 mg/100 kcal) of phosphate is recommended. ESPGHAN 2010
Bone demineralization at discharge
Pre- & postnatal time course of volumetric bone mineral density (BMAD) with DEXA (713 measurements in 494 infants; Rigo J 2005)
Relationship between DEXA vBMD and gestational age

\[ y = 0.194 \times GA + 3.89; \ SD=0.86; \ n=106; \ r=0.617 \]
Relationship between SOS and gestational age

\[ \text{SOS} = 10.95 \times x + 2600.7; \text{SD} = \pm 95.4; n=146; r = 0.398 \]
Thank you for your attention
Neonatal Ca P Disorders

hypocalcemia  -Early: related to Ca intake→ provide Ca from the first day
            -Late: related to Vit D deficiency, not to PTH
deficiency→ provide Vit D + Ca from the first day

Hypercaclemia: related to P deficiency→ provide P from the first day, adapt Ca/P ratio

Hypophosphatemia: TrP>95%, related to P deficiency → provide P from the first day, adapt Ca/P ratio

Preterm osteopenia – light: relative physiological phenomena in relation to postnatal adaptation
            – severe with risk of fracture: inadaptation of the Ca, P and Vit D intake. Prevented by actual parenteral and enteral recommendation
Interval references of sP conc in newborn infants