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Mineral metabolism in Preterm infants on Parenteral and Enteral Nutrition

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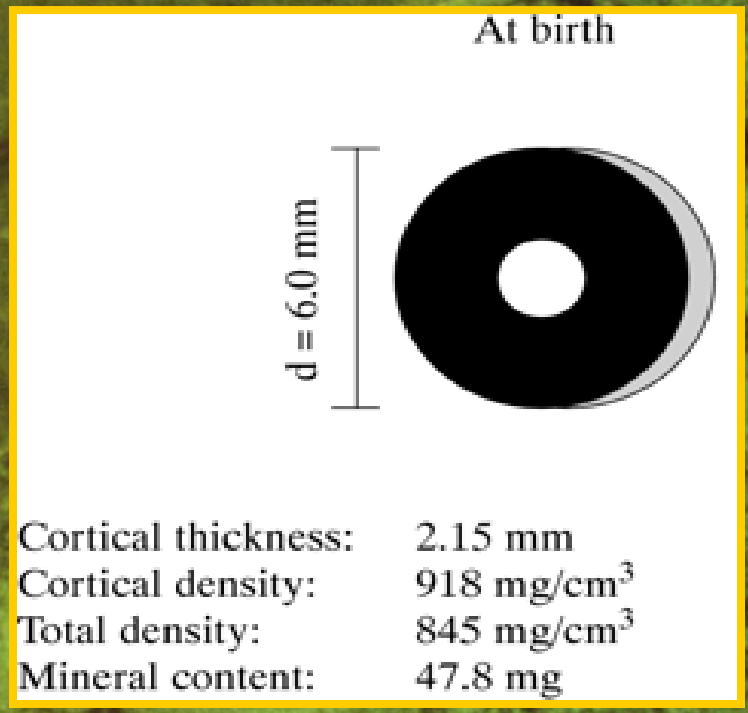
Assessment of bone growth and mineralisation during the fetal life

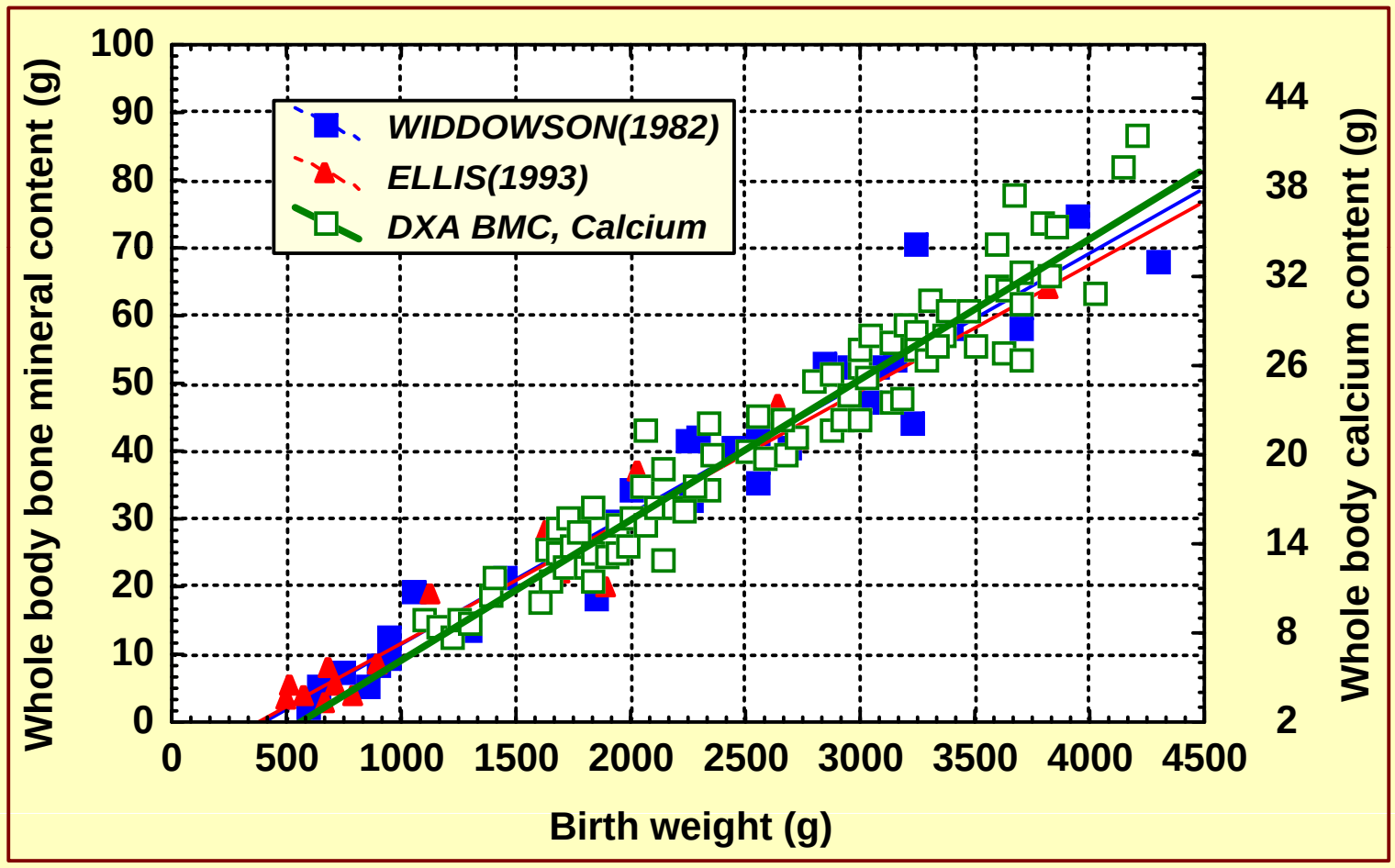
Factors influencing bone growth and mineralisation during the fetal life

- 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.

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



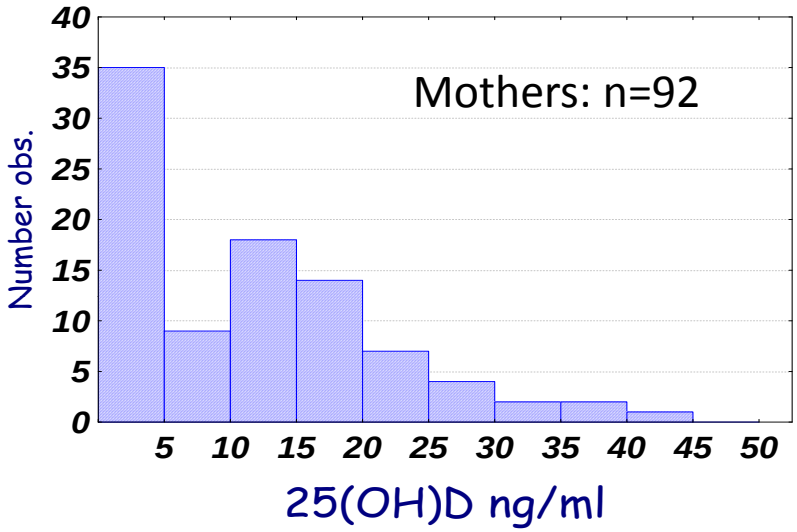
For DEXA, Ca content was calculated as Ca= 0.456*BMC+1.56
Picaud et al, AJCN 1996:63:157-63

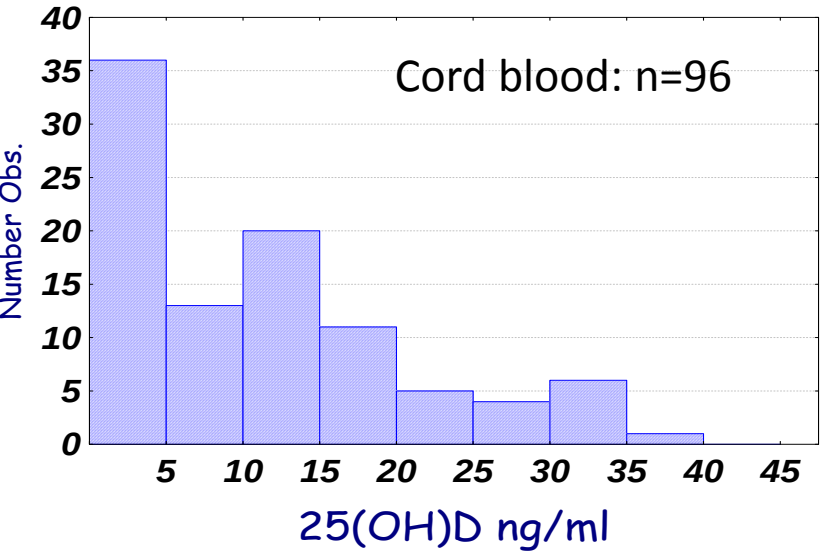
Ca, P and Vit D requirements ,for preterm infants

	Fetal accretion (mg/kg*d)	Human milk supply (mg/kg*d)
Calcium	120	50
Phosphorus	70	25
Magnesium	3	5

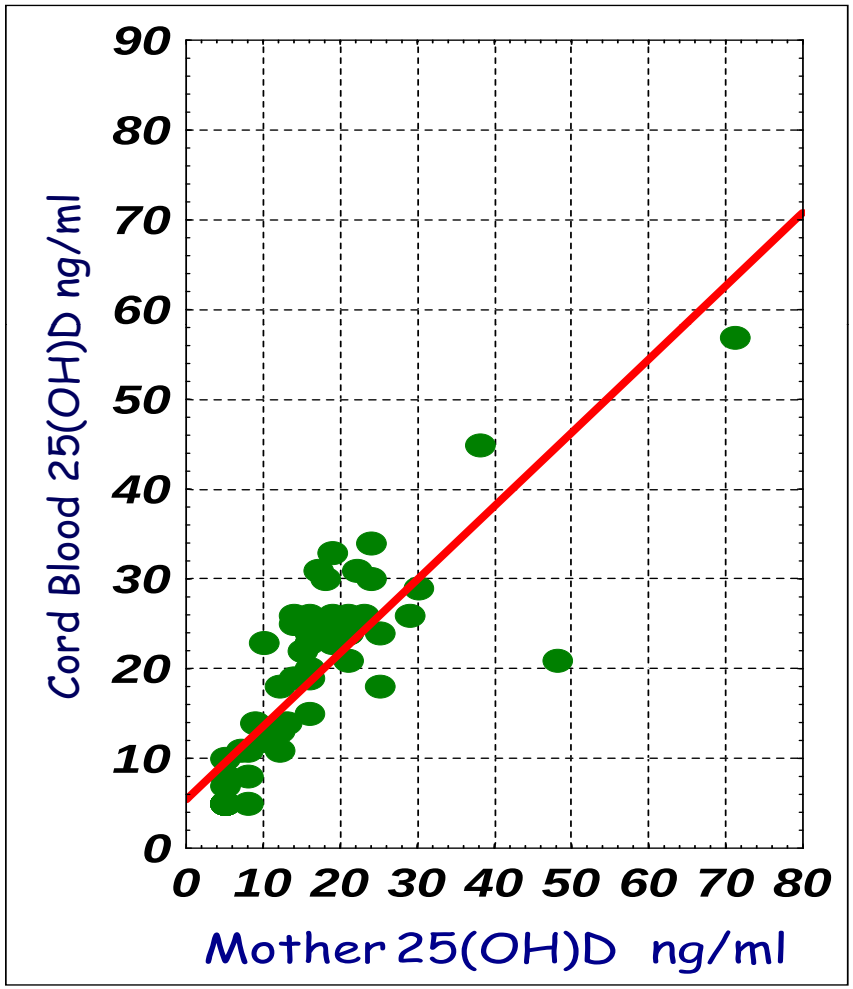
Ca, P and Vit D requirements ,for preterm infants

Fetal Vit D status





Mother to infant relationship



C Pieltain & J Rigo 2008

Fetal Ca Accretion

Transplacental flux

120 mg/kg*d

In utero

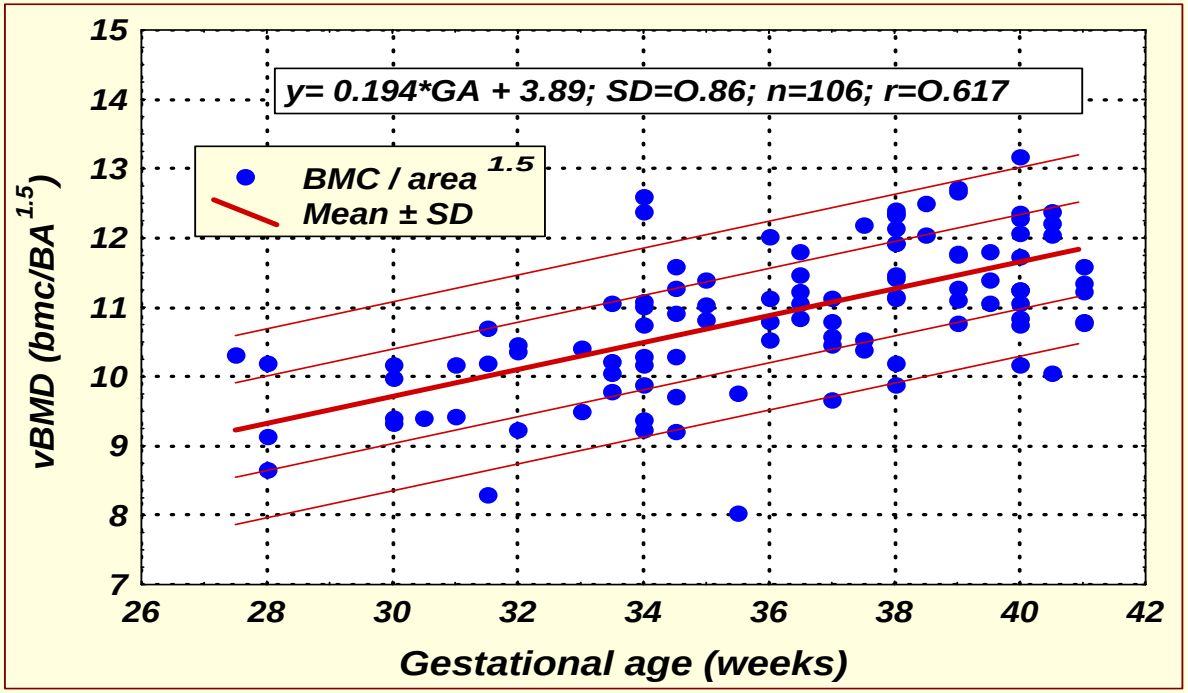
Plasma Pool

Bone

growth and modeling

vBMD ↗

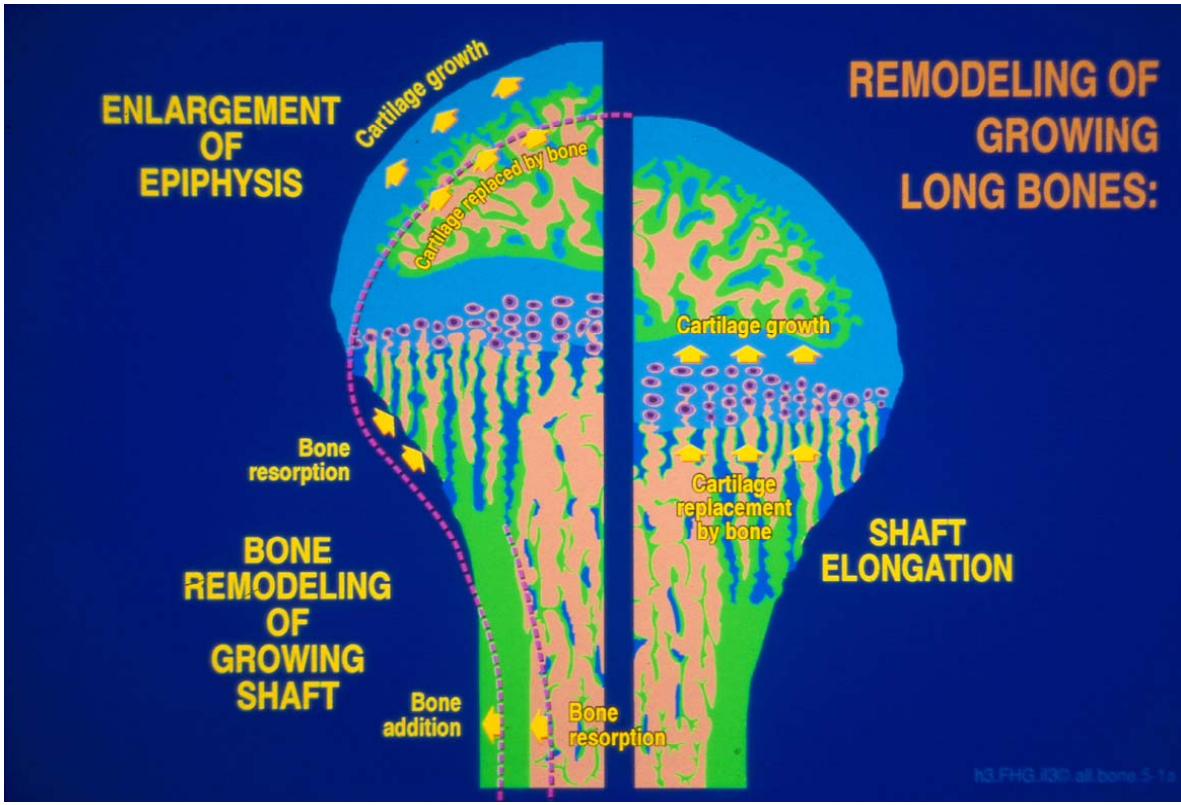
Reference values of vBMD according to gestational age in preterm and term infants at birth




Post-natal Mineral Requirements
NESTLÉ
?
?

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[1] *Salle BL & al AJCN 2000;71:1317S*

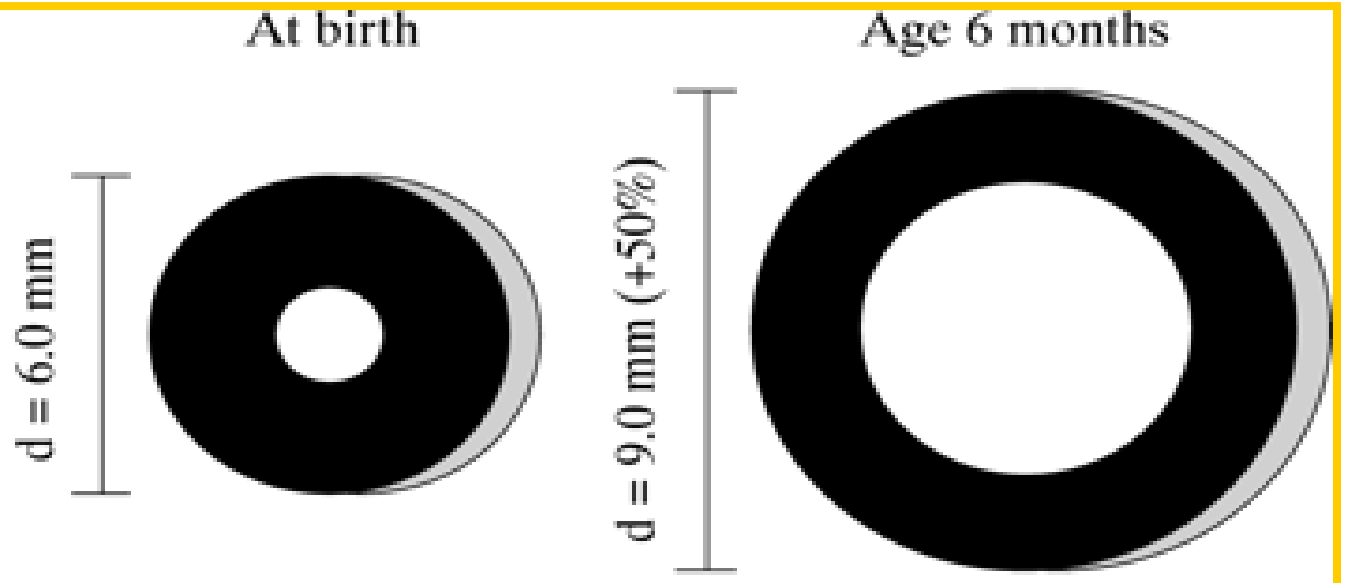
	Calcium	PTH(1–84)	cPTH	DBP
	mmol/L	*pmol/L*	*pmol/L*	*µ mol/L*
Cord serum	2.24 ± 0.09	11 ± 3	48 ± 8	4.43 ± 0.37
Day 1	1.94 ± 0.04[2]	66 ± 11[2]	125 ± 15[2]	4.40 ± 0.34
Day 2	1.85 ± 0.05[2]	87 ± 11[2]	168 ± 5[2]	4.96 ± 0.23
Day 5	2.22 ± 0.05	67 ± 9[2]	152 ± 16[2]	6.21 ± 0.26[2]
Day 10	2.45 ± 0.06	23 ± 4	69 ± 6	6.03 ± 0.30[2]
Day 30	2.44 ± 0.05	38 ± 7	80 ± 11	5.16 ± 0.23

[1] ± 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 radialimmunodiffusion assay (65).

[2]Significantly different from cord serum, $P < 0.05$ (one-factor ANOVA for repeated measures followed by Scheffe F test).

Normal postnatal changes in the cross section of the femoral diaphysis

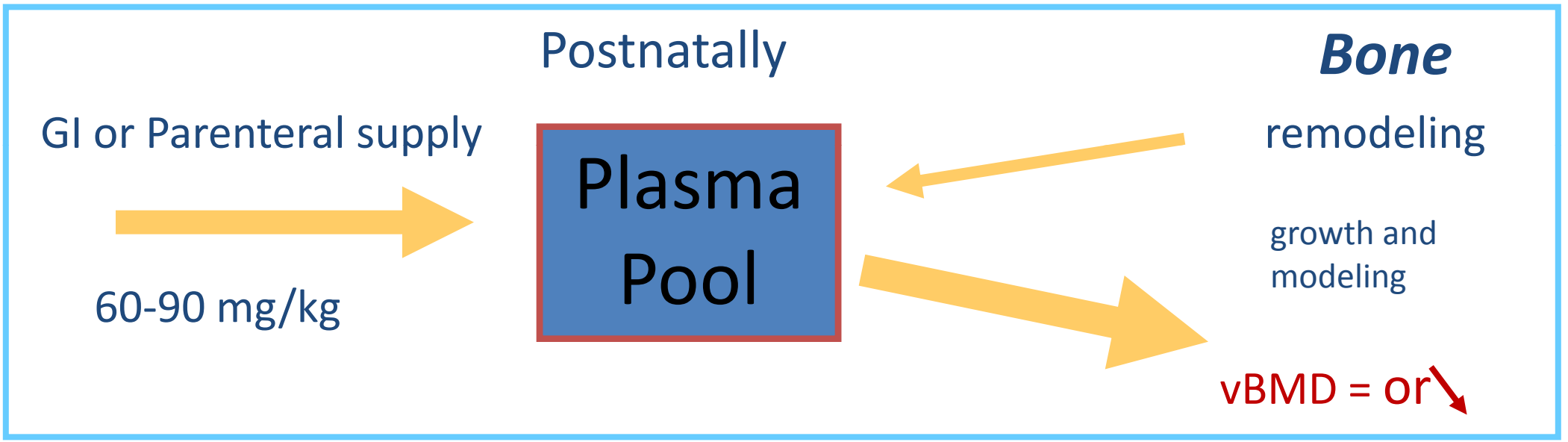
F Rauch, E Schoeneau Arch Dis Child FN 2002:86;F82-85



Cortical thickness:	2.15 mm	2.00 mm (–8%)
Cortical density:	918 mg/cm^3	855 mg/cm^3 (–7%)
Total density:	845 mg/cm^3	592 mg/cm^3 (–30%)
Mineral content:	47.8 mg	75.3 mg (+58%)

The increase of Ca turnover could reduce the nutritional needs ?

Physiological change in mineral requirements

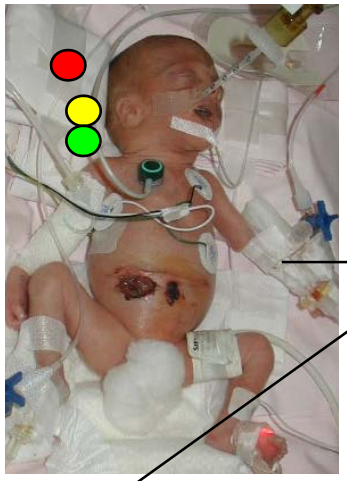


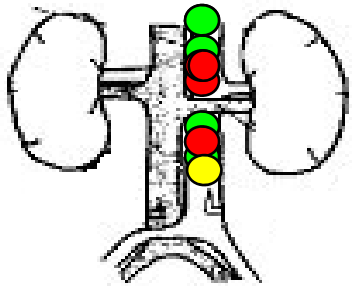
The increase of Ca turnover could reduce the nutritional needs ?

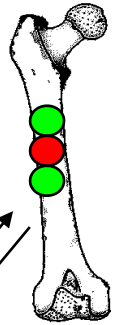
Calcium & Phosphorus Physiology in Parenteral Nutrition

Ca P & AA in Parenteral Nutrition

- Calcium : Phosphore & AA directly Available for metabolism.
- Calcium & Phosphorus content are limited due to their poor solubility





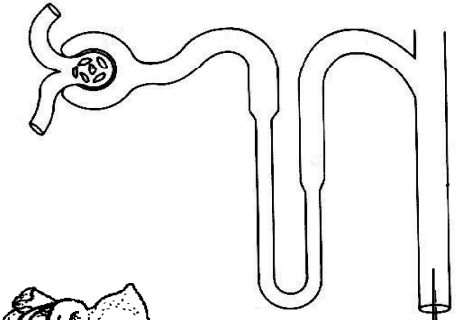


Mineralization

As hydroxyapatite
$[Ca_{10}(PO4)_6(OH)_2]$

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

Urinary excretion



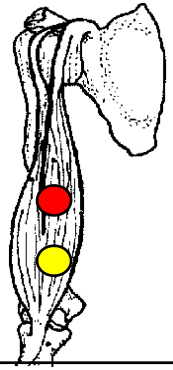
Phosphaturia

Major 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 (AA) retention
Nitrogen/P Ratio = 15/1

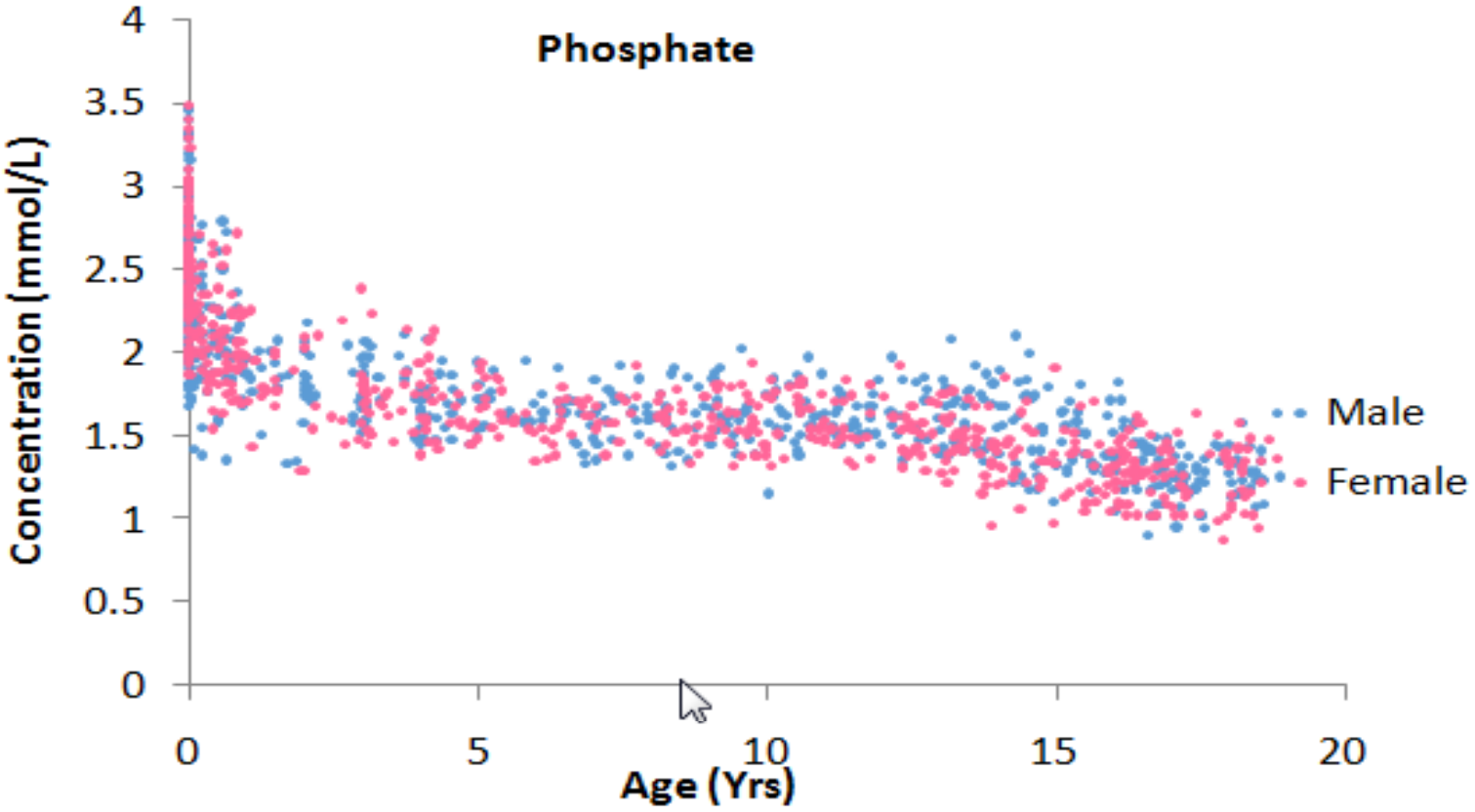
Blood Pool

Calcium : 50% Ca_i (biologically active)
40% bound to protein
10% complexed with org/inorg ac
Régul : PTH ↗, vit D ↗, calcitonin ↘

Phosphore : 2/3 organic phosphorus
1/3 inorganic phosphorus
Regul : PTH ↘, vit D ↗, FGF23 ↘

Calcium
Phosphorus
Protéines

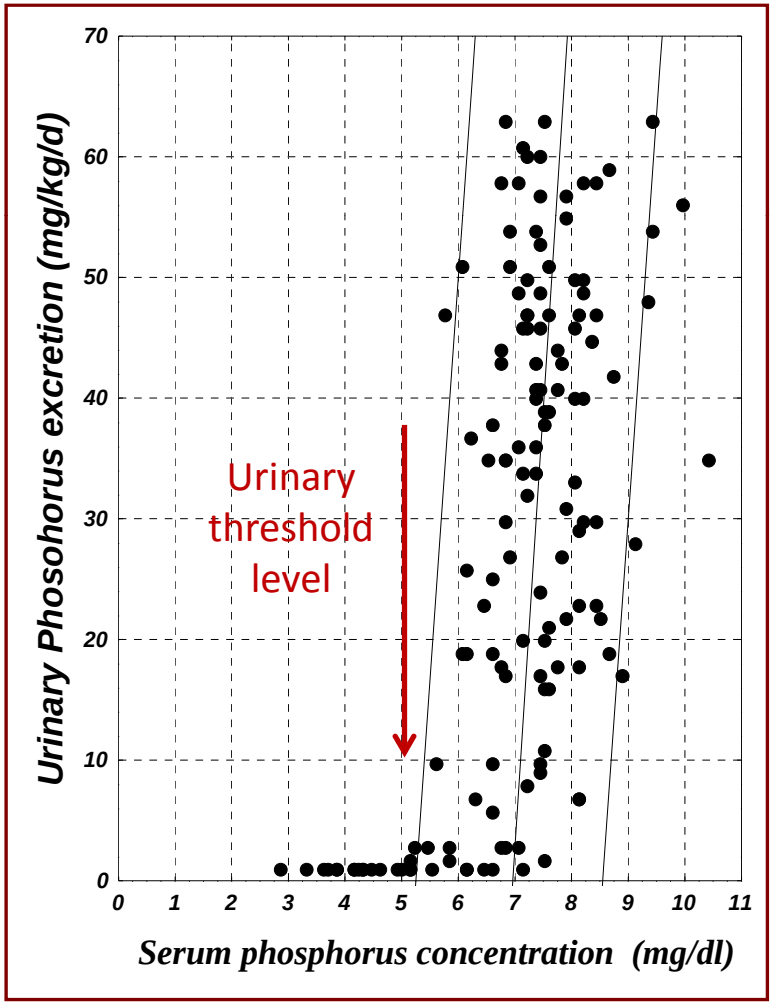
Reference value for Phosphate serum concentration according to age



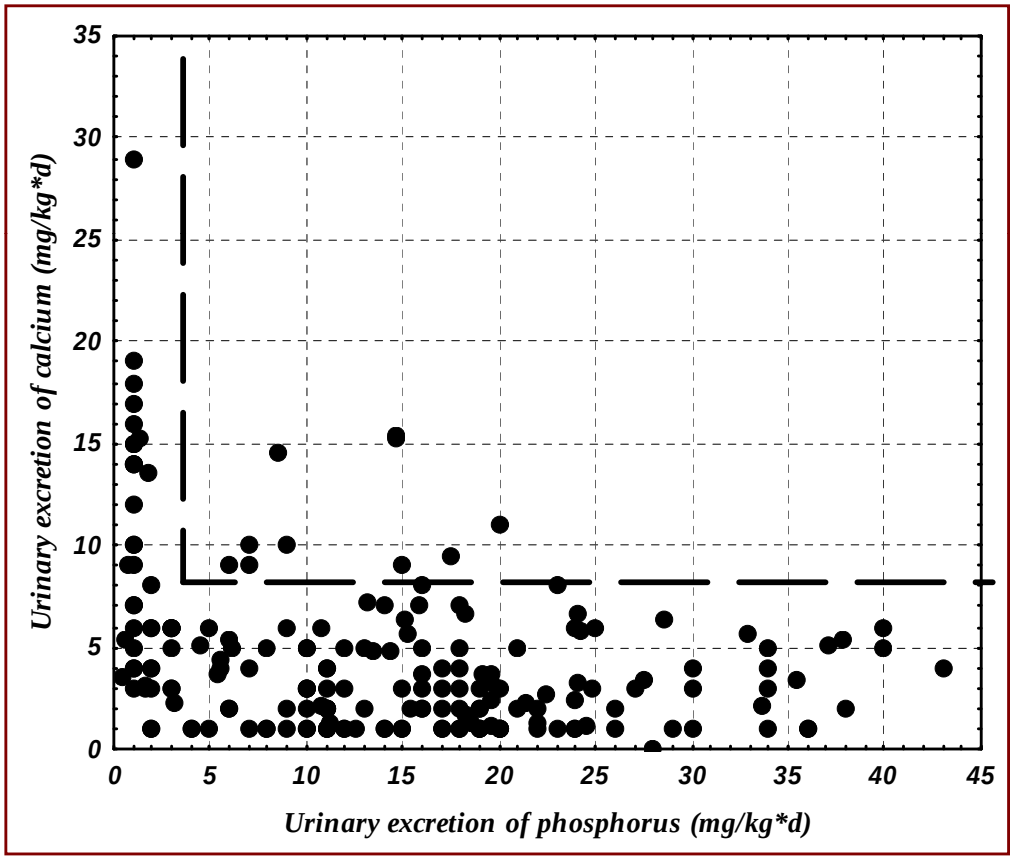
Colantonio & al

Ca, P and Vit D requirements ,for preterm infants

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



Relationship between urinary excretion of calcium and urinary excretion of phosphorus in preterm infants (n=198).

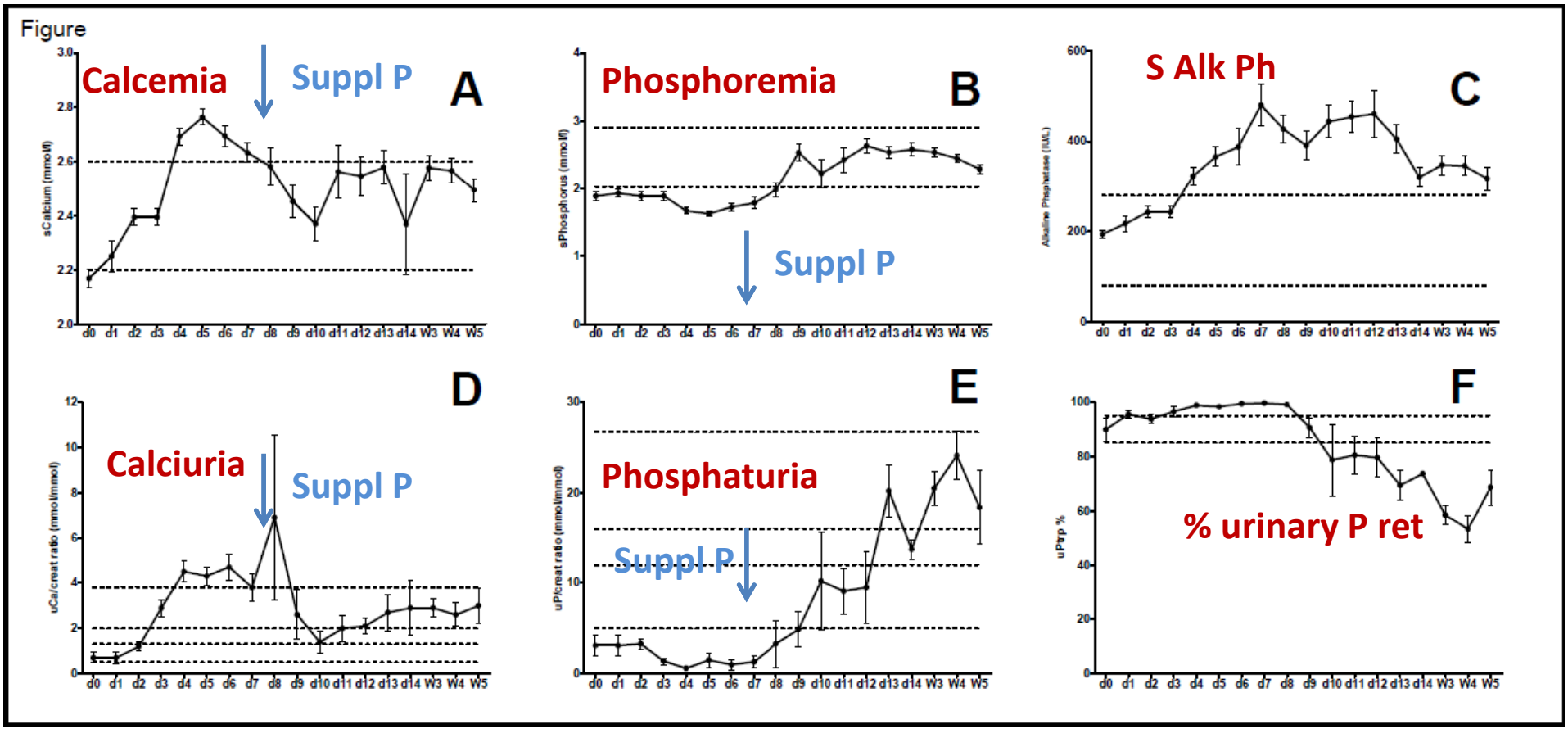


Hypercalciuria (>10 mg/kg*d) is related to low phosphate excretion (<3mg/kg*d). Whereas, urinary excretion of calcium below 8 mg/kg*d is generaly observed in preterm infants with a phosphorus excretion over 10-15 mg/kg*d.

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



Early hypophosphatemia in preterm infants receiving aggressive parenteral nutrition. Brener D J Perinatol. 2015 Sep;35(9):712-5

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

(mg/kg*d)	
Ca intake	100 ± 23
P intake	76 ± 18
Ca ur.	5.6 ± 4.7
P ur.	18 ± 14
Ca retention	94 ± 20 (94%)
P retention	58 ± 17 (76%)

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 need = Ca intake / 2.15 + (AA intake – 1.3) * 0.8 * 12.3

Magnesium in parenteral nutrition in VLBW infants

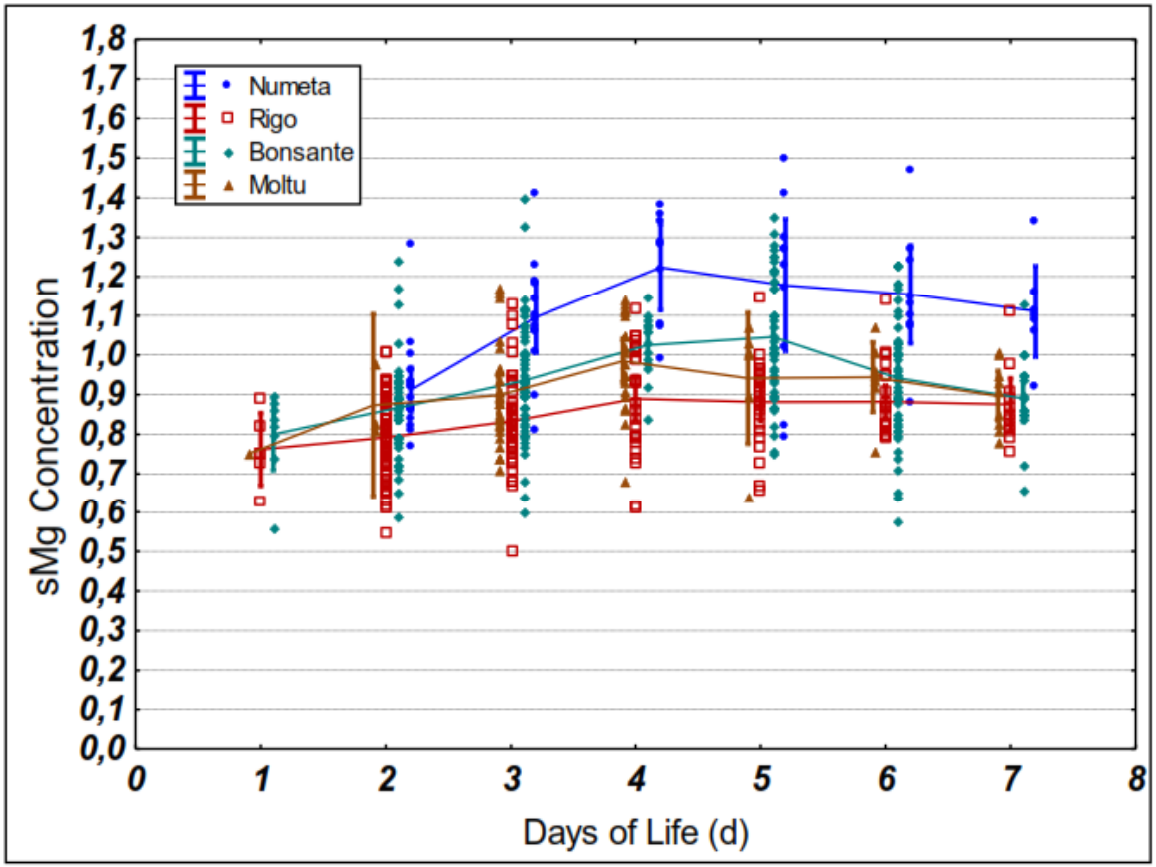
1. In 2013, 14 case reports of hypermagnesemia have been reported in VLBW infants on parenteral nutrition providing a maximum Mg intake of 0.55 mmol/kg*d, in the range of the recommended values. Serum magnesium levels in the 14 infants ranged from 1.025 to 1.5 mmol/l without any symptoms or serious adverse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

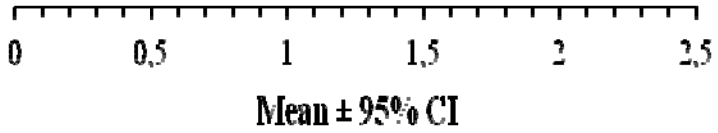


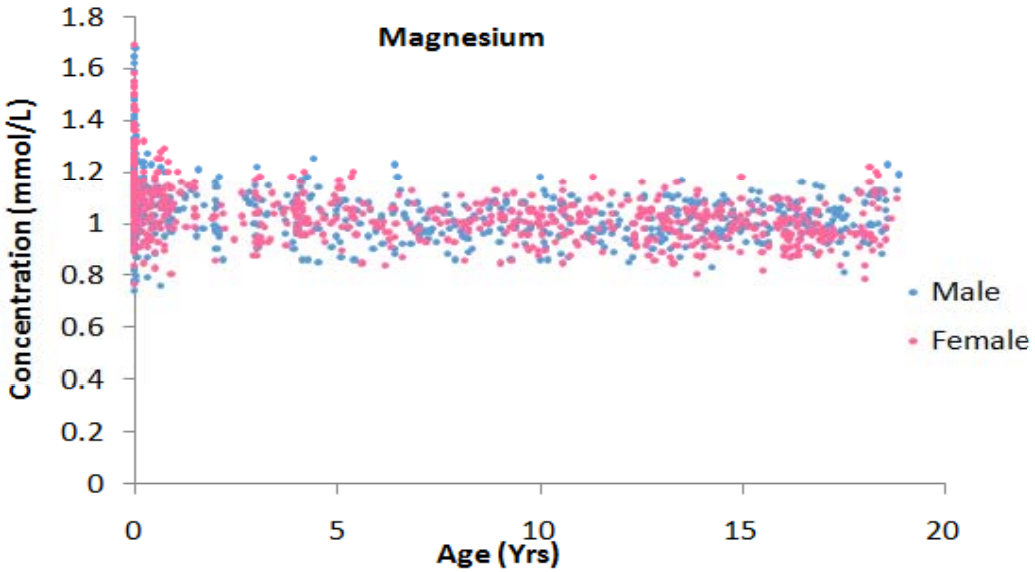
Rigo & al 2016 submitted

meta-analysis of magnesium concentrations in newborns (mmol/L)

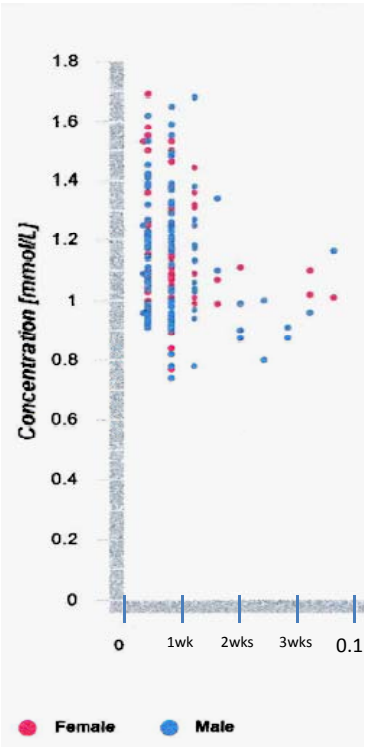
Population, *timing*	n	Estimated mean and reference interval	Mean (95% CI)
Healthy newborns without magnesium supplementation during pregnancy, *at birth*	2642		0.76 (0.52, 0.99)
Healthy newborns without magnesium supplementation during pregnancy, *first week*	928		0.87 (0.50, 1.23)
Very-low-birth-weight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

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%
Proximal Intestin
Vit-D, Ionisation (low pH) ↗

Phosphore : About 90%
Duod., jéjunum > iléon, colon
Less Vit-D related

Blood Pool

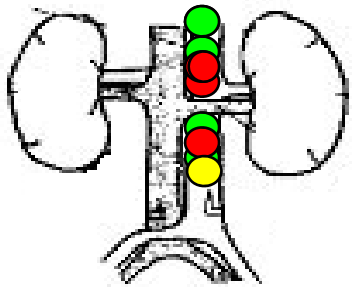
Calcium :

50% Ca_i (biologically active)
40% bound to protein
10% complexed with en org/inorg ac
Régul : PTH ↗, vit D ↗, calcitonin ↘

Phosphore :

2/3 organic phosphorus
1/3 inorganic phosphorus
Regul : PTH ↘, vit D ↗, FGF23 ↘

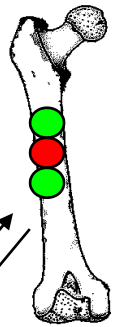
Calcium
Phosphorus
Protéines

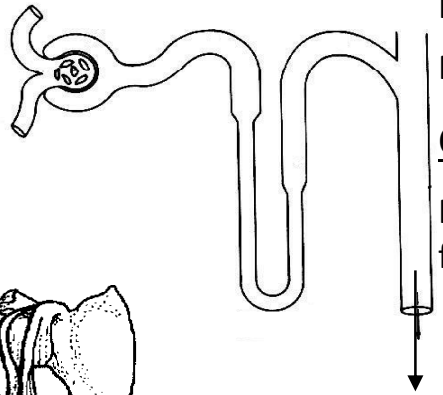


Mineralization

As hydroxyapatite
$[Ca_{10}(PO4)_6(OH)_2]$

Ca/P Ratio = 2.15





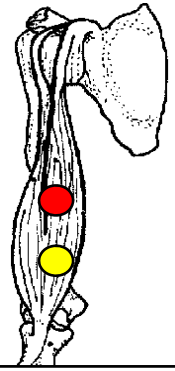
Phosphaturia

Main mecanism 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

	HM and HMF			Preterm formulas			
CALCIUM (mg/kg/d)	n=36	n=22	n=23	n=31	n=37	n=27	n=20
Intake	56	86	138	81	101	135	166
Stool	21	26	56	40	47	73	103
Absorption	35	59	82	41	54	62	63
Urine	7	6	5	2	3	5	5
Retention	28	53	77	39	51	57	58
Net absorption(%)	64	69	60	50	54	46	38

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 (%).

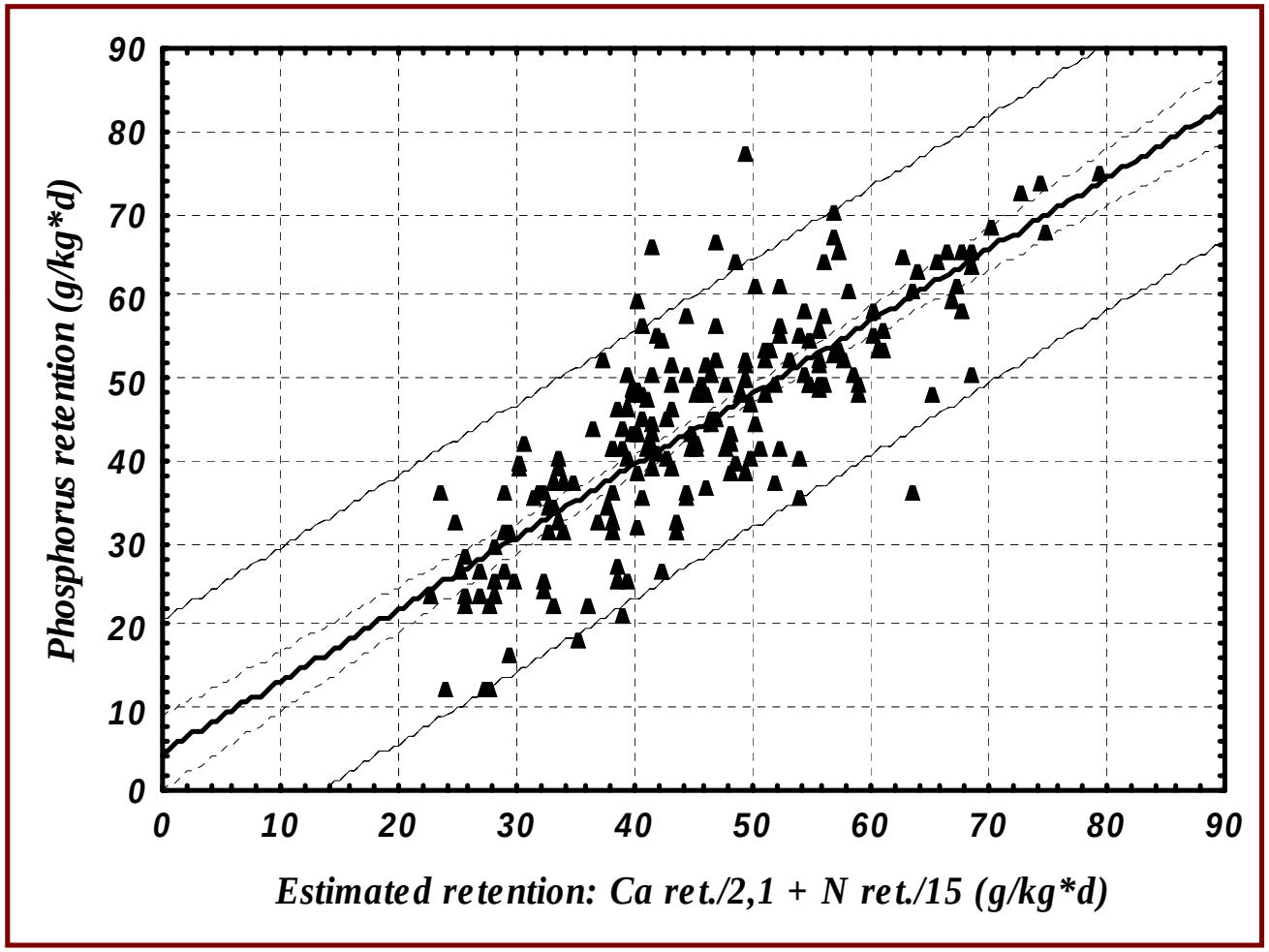
Phosphorus absorption and retention in preterm infants fed human milk without or with human milk fortifier, and preterm formulas

	HM and HMF			Preterm formulas			
PHOSPHORUS (mg/kg/d)	n=36	n=22	n=23	n=31	n=37	n=27	n=20
Intake	40	56	85	59	69	86	95
Stool	3	4	6	7	5	13	34
Absorption	37	52	79	53	63	73	60
Urine	8	6	19	14	18	22	9
Retention	29	46	60	38	45	51	51
Net absorption %	92	92	93	89	92	85	63

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

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*j) = 0,87*estimated retention (g/kg*d) + 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

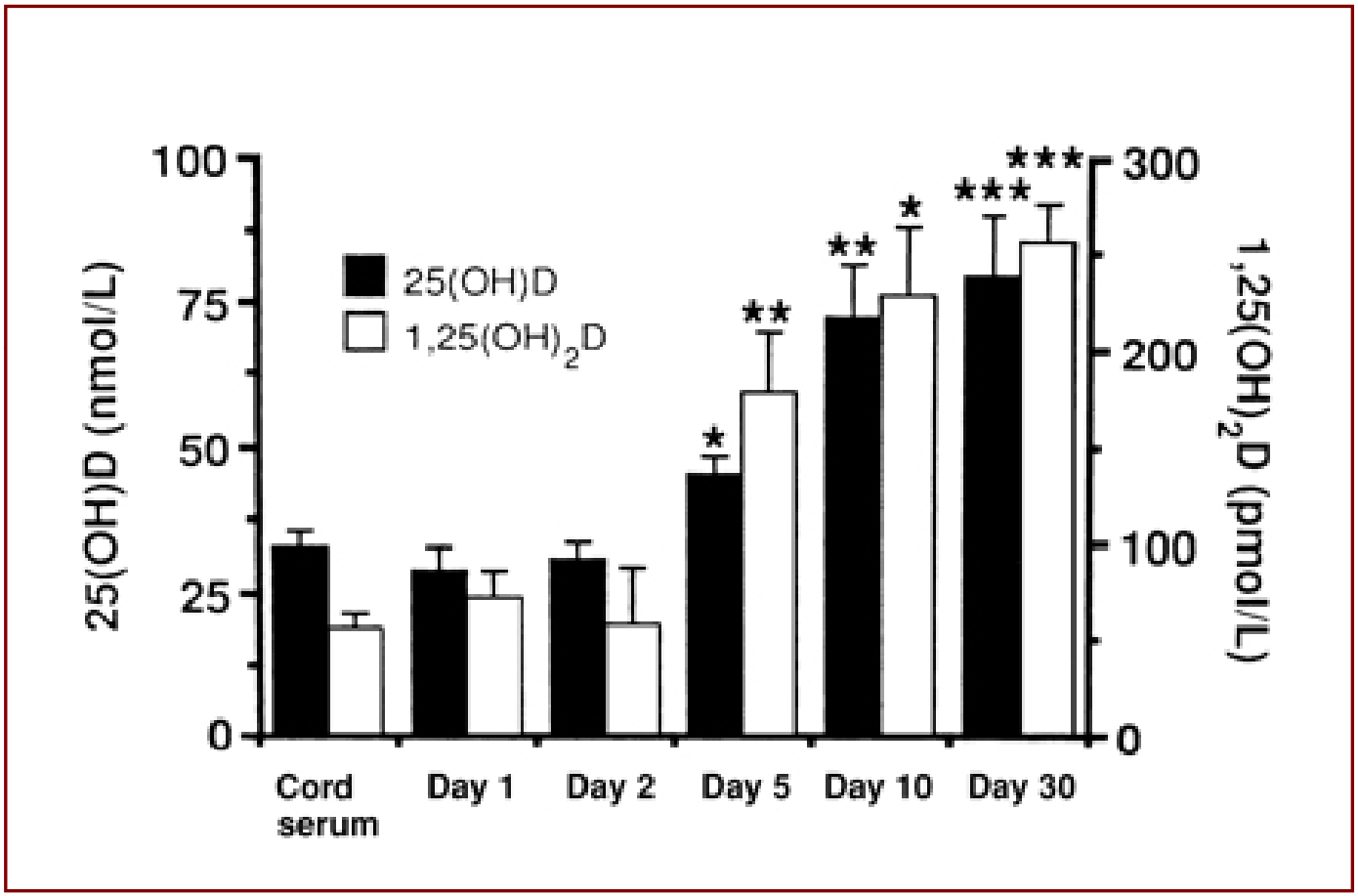
Conclusions: Calcium

- 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 availlable 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)$_2$D] 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.*

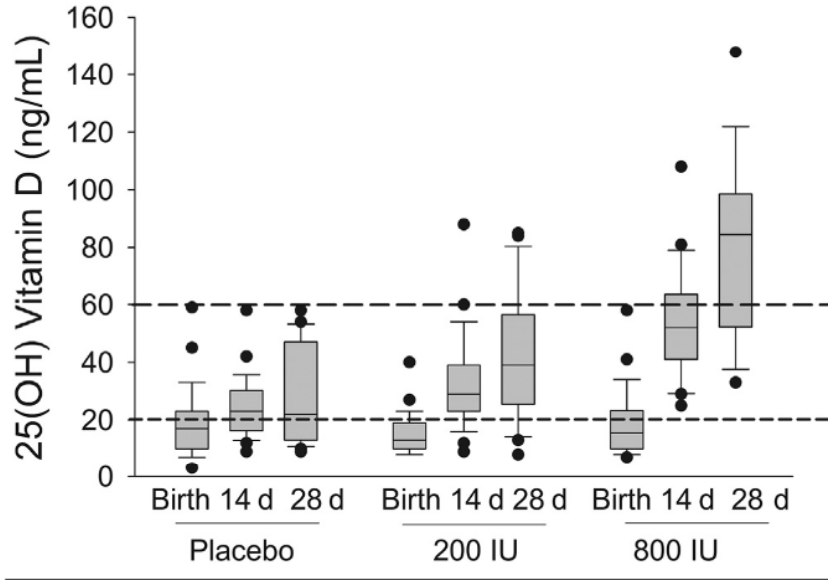
Salle BL 2000

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 t 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

Basis of the ESPGHAN revised recommendations for mineral requirements

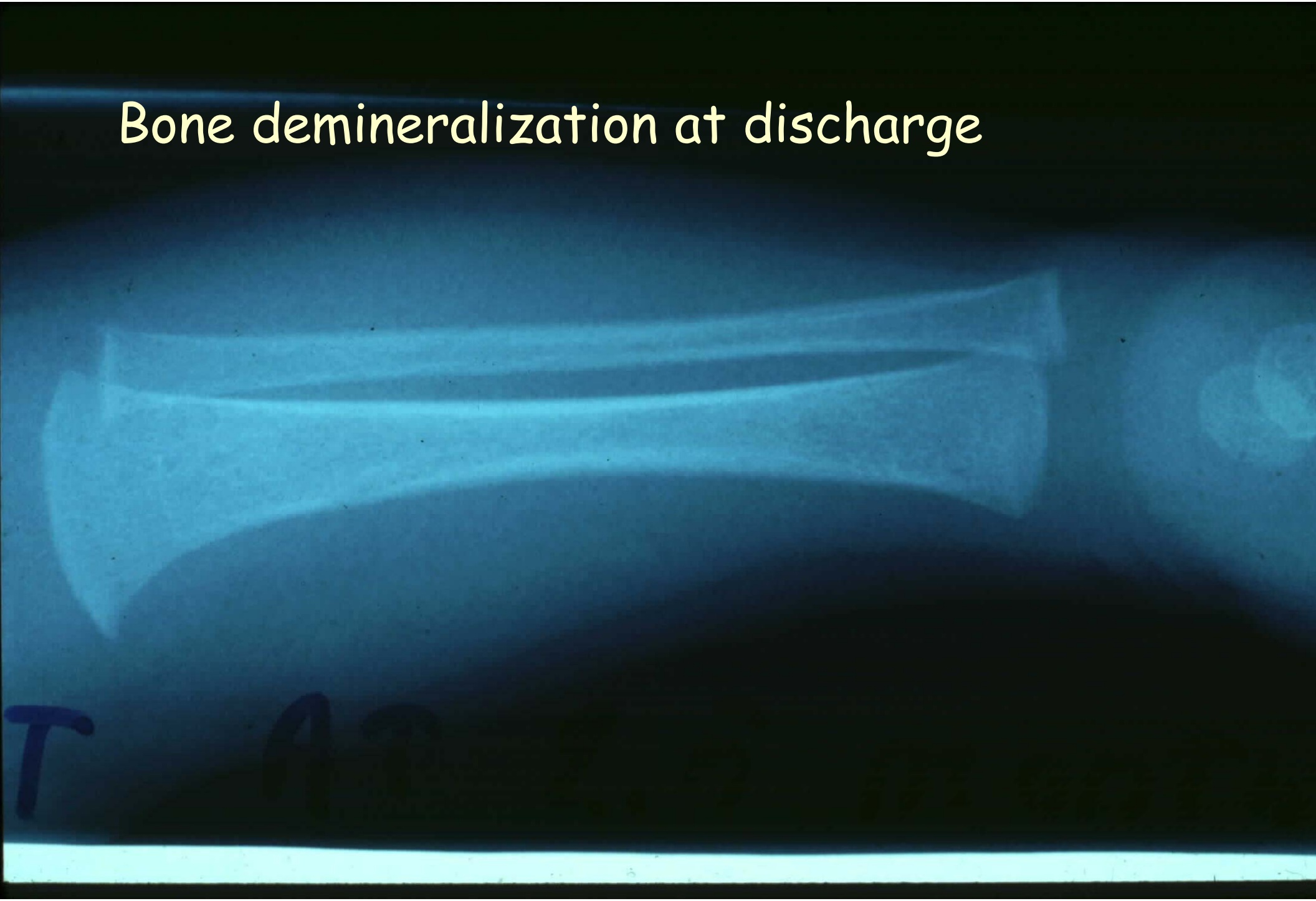
1. Previous recommendations are based on fetal mineral accretion.
2. Physiological changes in bone metabolism at birth, with a stimulation of the remodeling process inducing a spontaneous reduction in bone mineral density.
3. Mineral balances show limited absorptive capability of the gastrointestinal 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

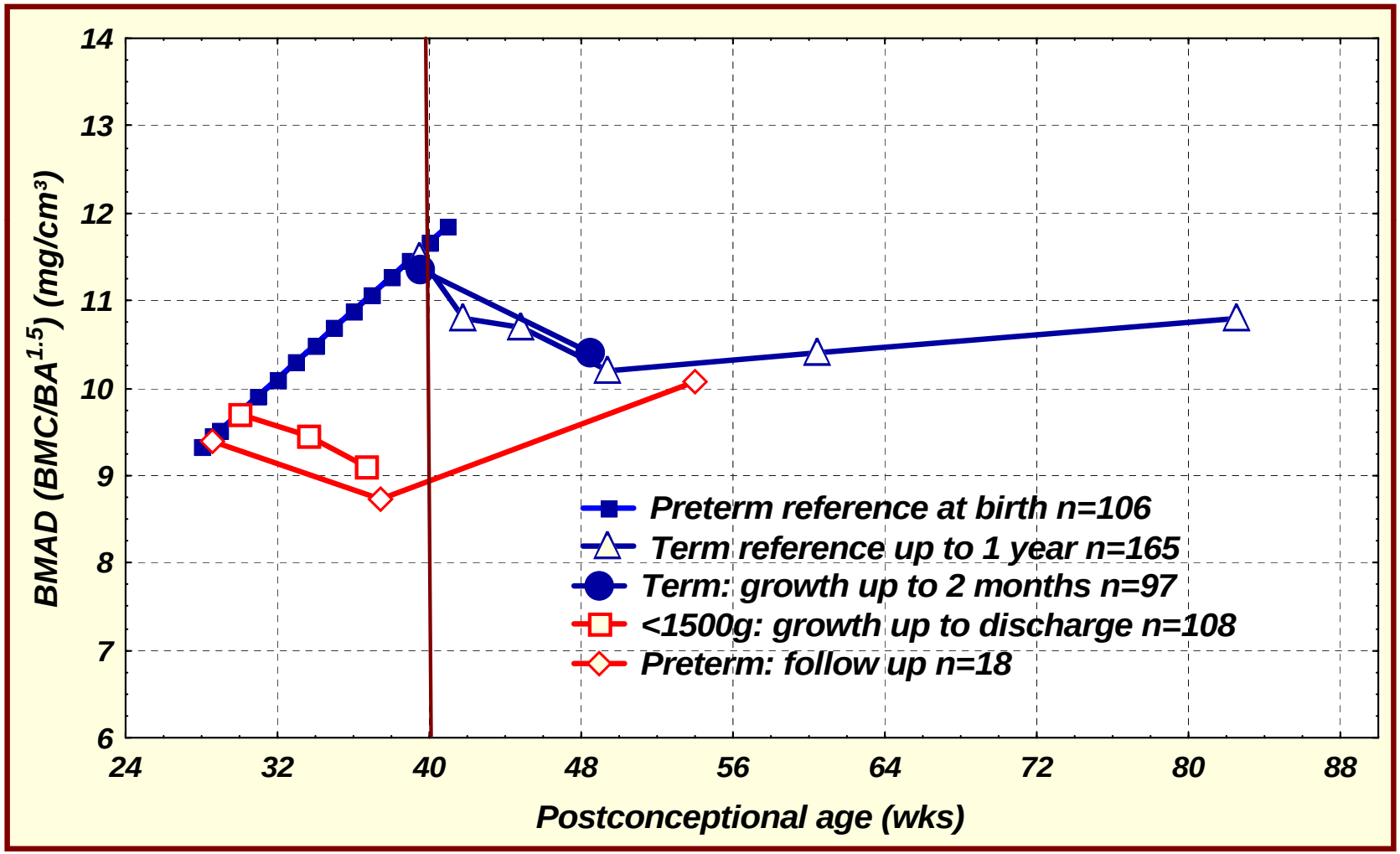
	ESPGHAN 2010		Tsang 2005	Klein 2002	ESPGHAN 1987
	/kg/j	/100 kcal	/100 kcal	/100 kcal	/100 kcal
Ca (mg) - ELBW - VLBW	120-140	110-130	 77-200 67-169	123-185	70-140
P (mg) - ELBW - VLBW	60-90	55-80	 46-127 40-108	82-109	55-80
Vit D (IU/j) - LBW(IU/100 kcal) - VLBW	800-1000		 115-364 100-308		

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 140mg *kg^{-1}*day^{-1} (110–130 mg/100 kcal) of highly bioavailable calcium salts and 60 to 90mg kg1 day1 (55–80 mg/100 kcal) of phosphate is recommended. ESPGHAN 2010

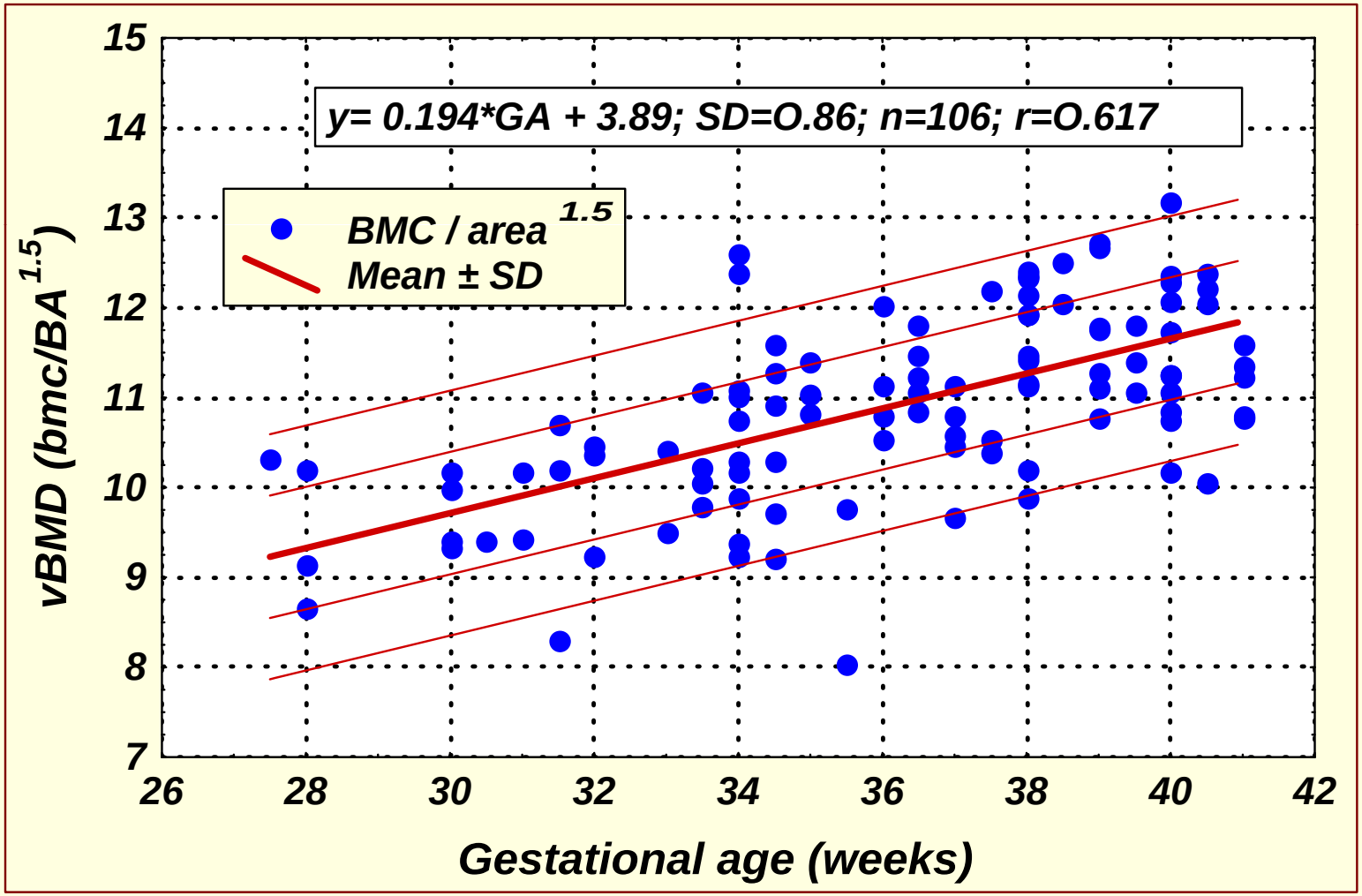
Bone demineralization at discharge



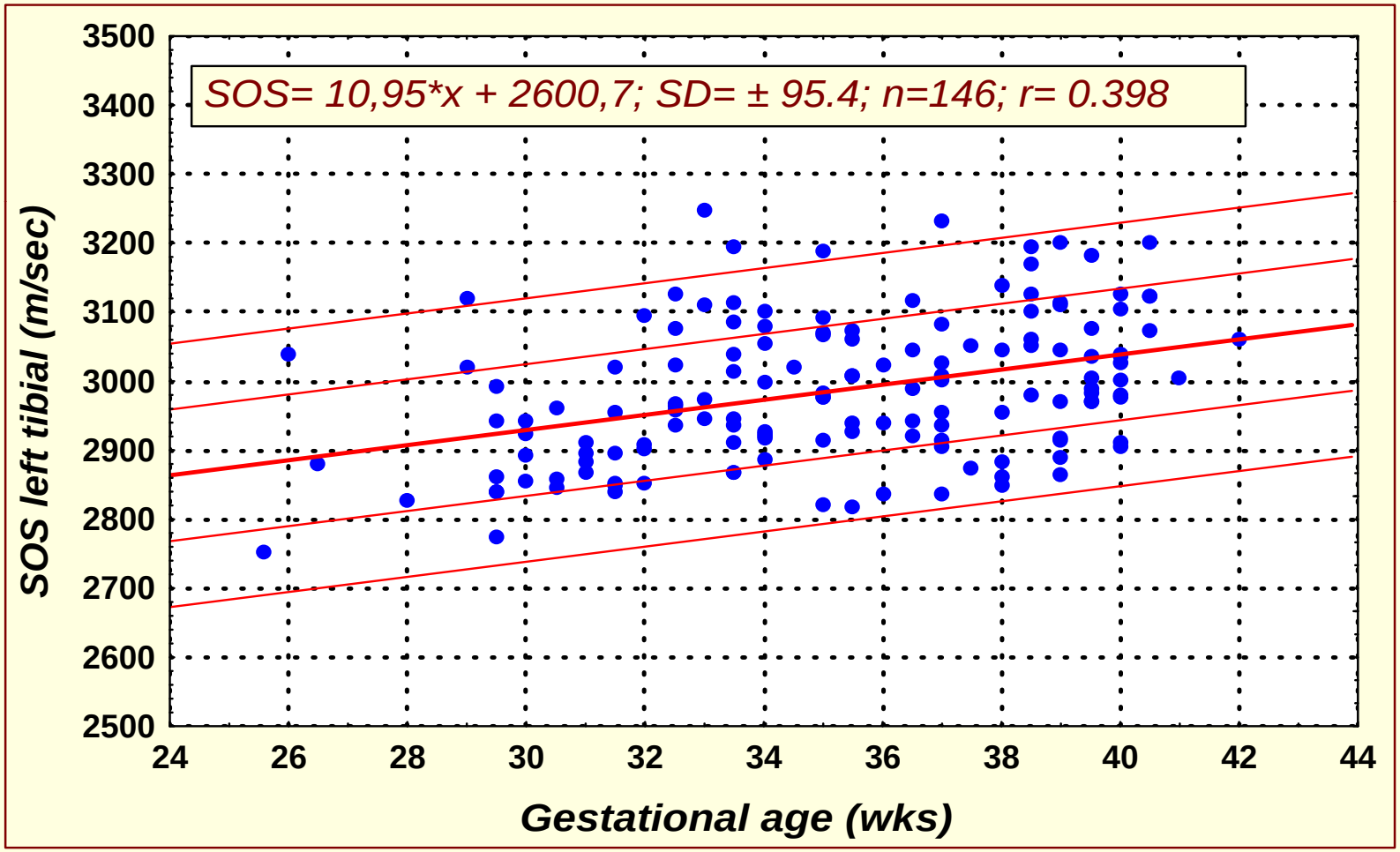
Pre- & postnatal time course of volumetric bone mineral density (BMAD) with DEXA (713 measurements in 494 infants; Rigo J 2005)



Relationship between DEXA vBMD and gestational age

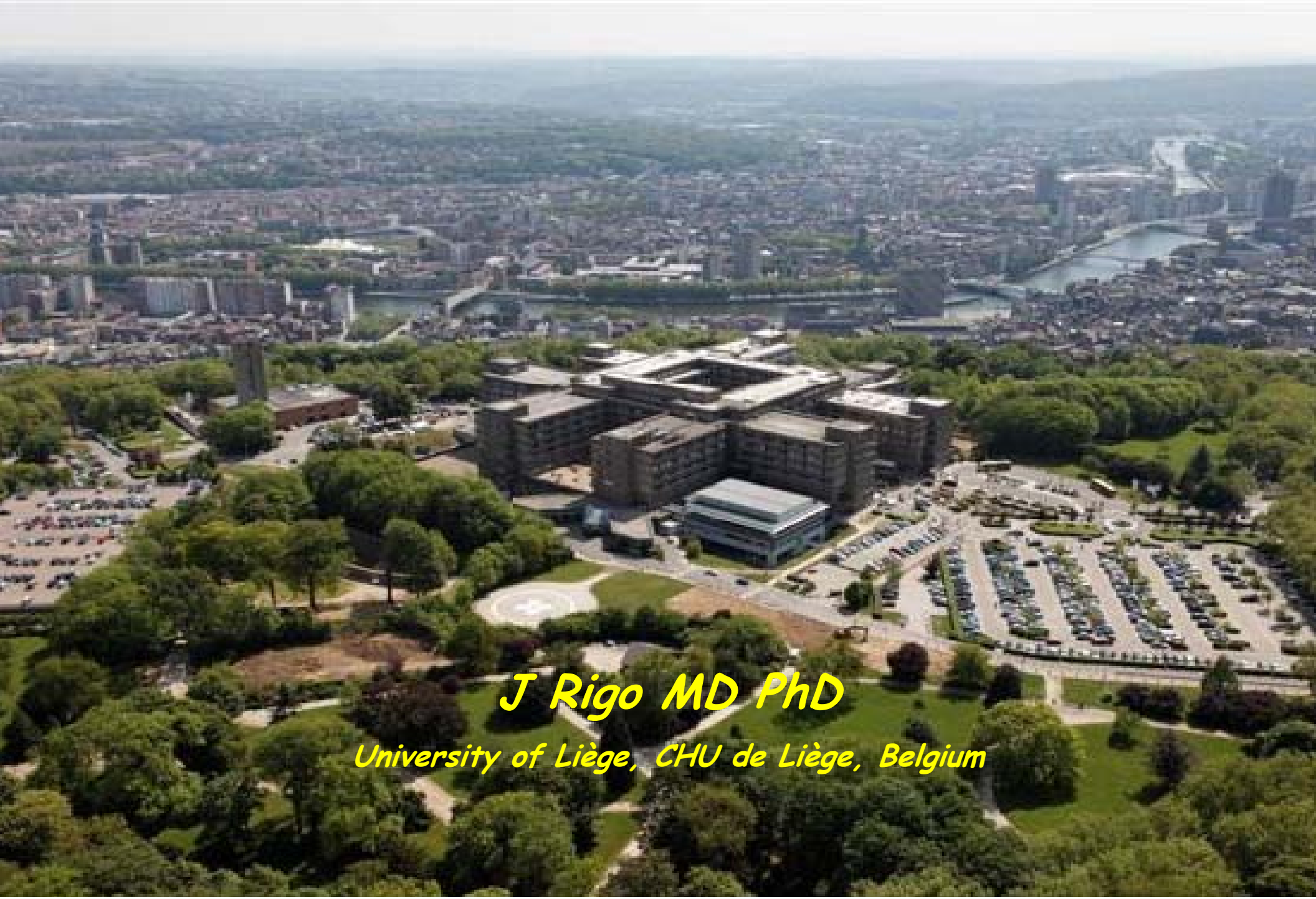


Relationship between SOS and gestational age




Thank you for your attention


FIN


J Rigo MD PhD
University of Liège, CHU de Liège, Belgium

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

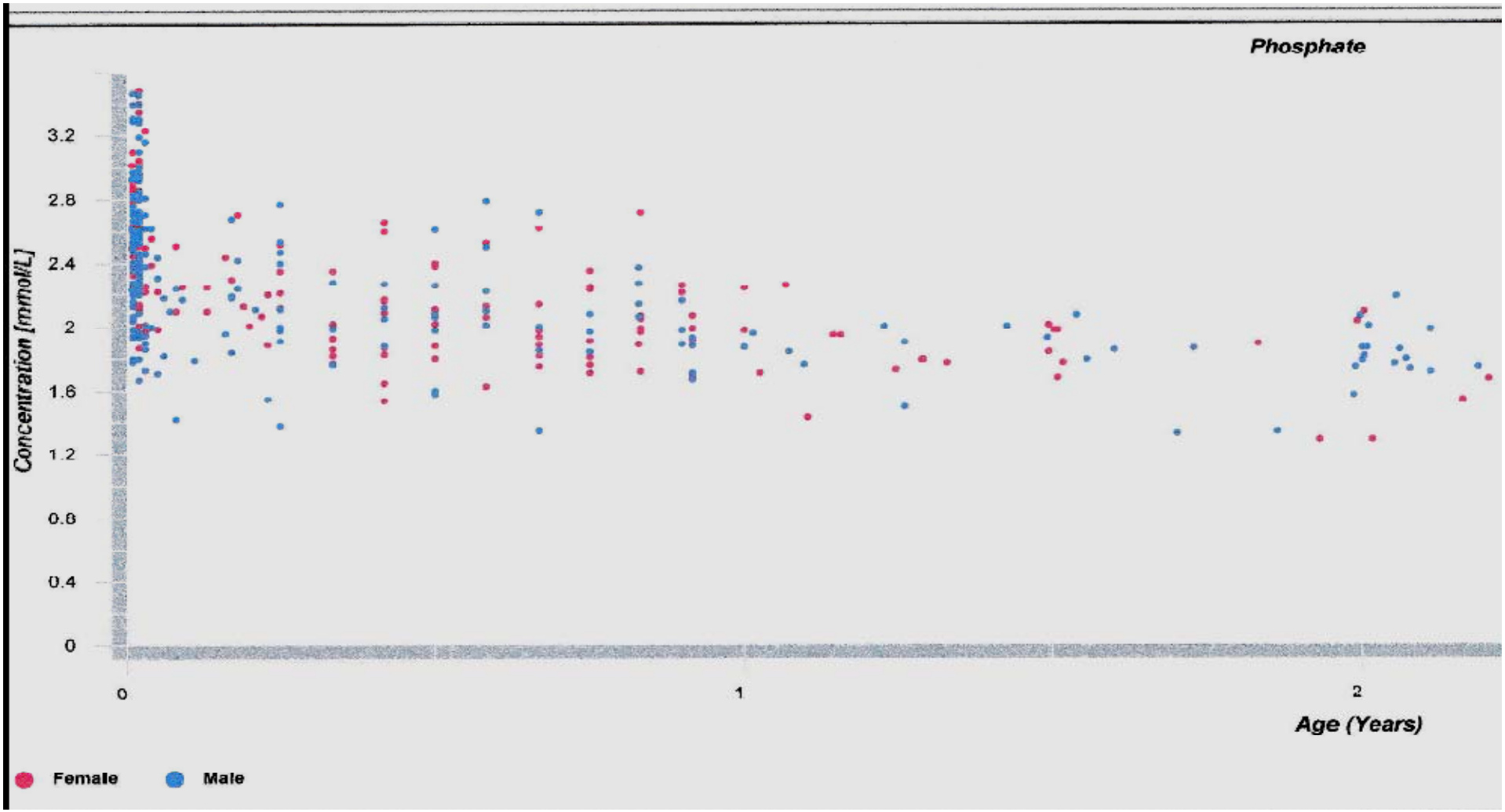
Hypercalcemia: related to P deficiency→provide P from the first day, adapt Ca/P ratio

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



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