UNIVERSITY OF CALGARY

SOCIETY OF NEONATAL GASTROENTEROLOGY NUTRITION & GROWTH

NEONATAL GASTROENTEROLOGY & NUTRITION PROGRAM - CALGARY

Metabolic Bone Disease of Prematurity

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Society of Neonatal Nutrition Gut & Growth

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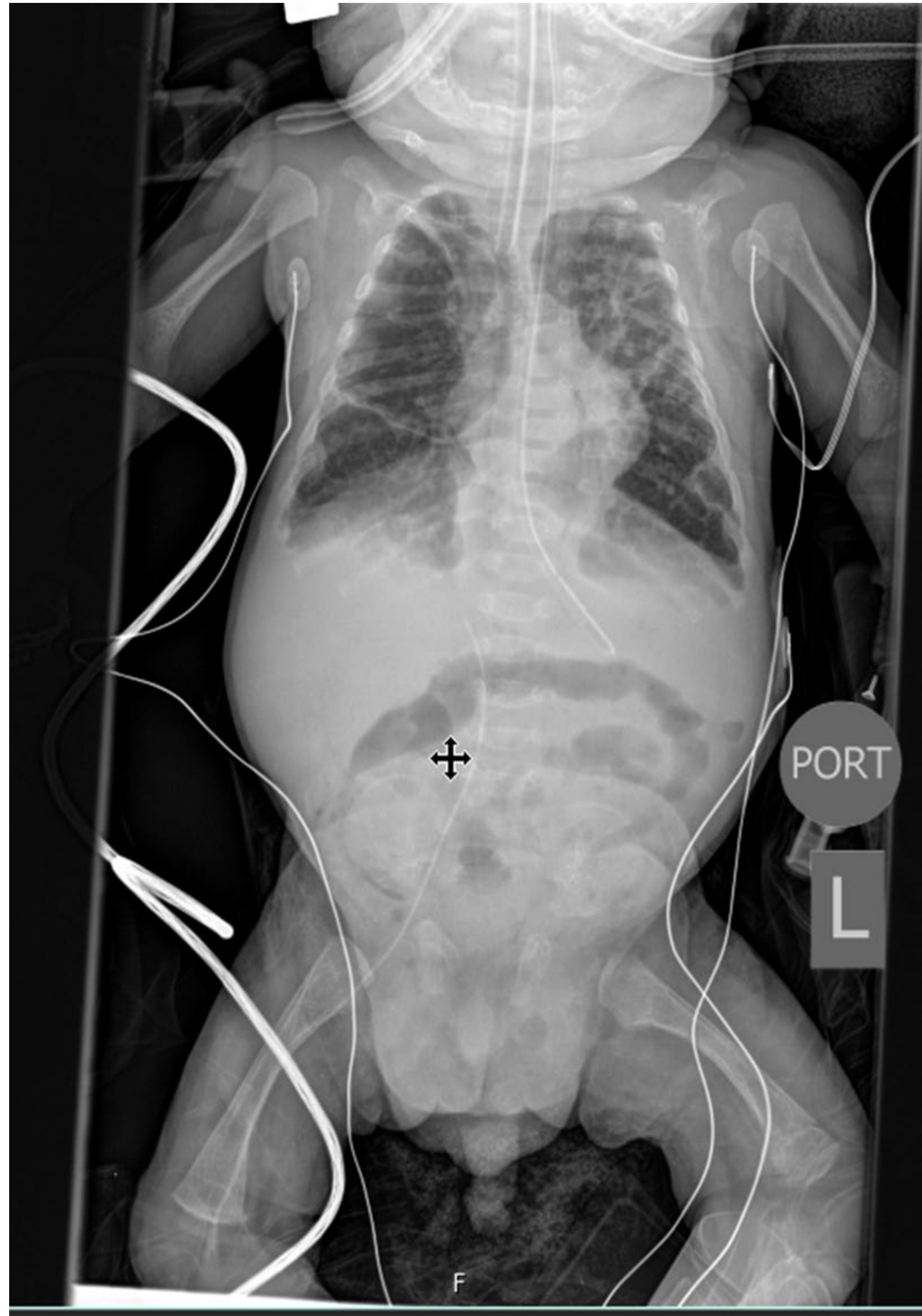
Objectives

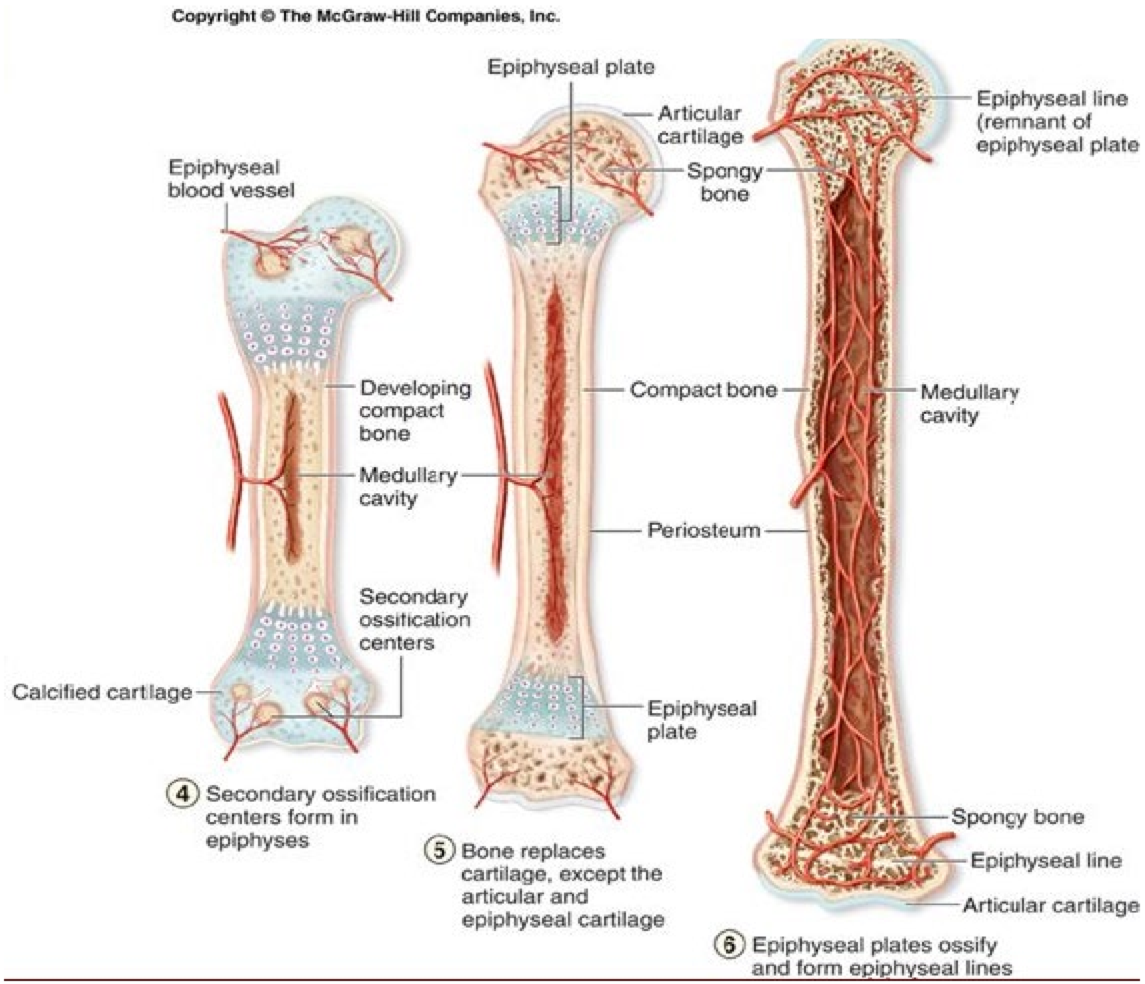
- Review bone accretion during fetal and early postnatal life
- Identify risk factors and screening strategies for metabolic bone disease
- Determine evidence-based interventions to support bone health in preterm infants

- Preterm 24+6 weeks
- DOL: 62 days
- Mededications:
  - DART x 1
  - Caffeine
  - Diuretics (short course)
- Late onset sepsis→ PICC → X ray



- How do you describe the skeleton?
  - Normal
  - Bone rarefaction
  - Subperiosteal bone formation
  - Metaphyseal alteration
  - Rib fracture
  - Long bone fracture

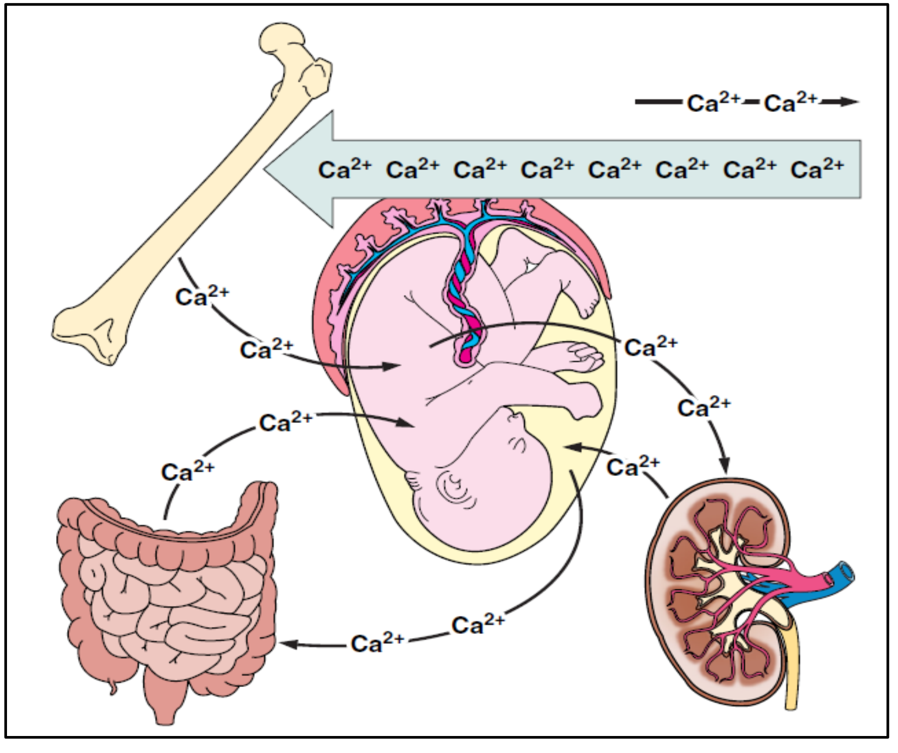
Bone development in fetal and early postnatal life



Bone formulation is a 2-phase process:

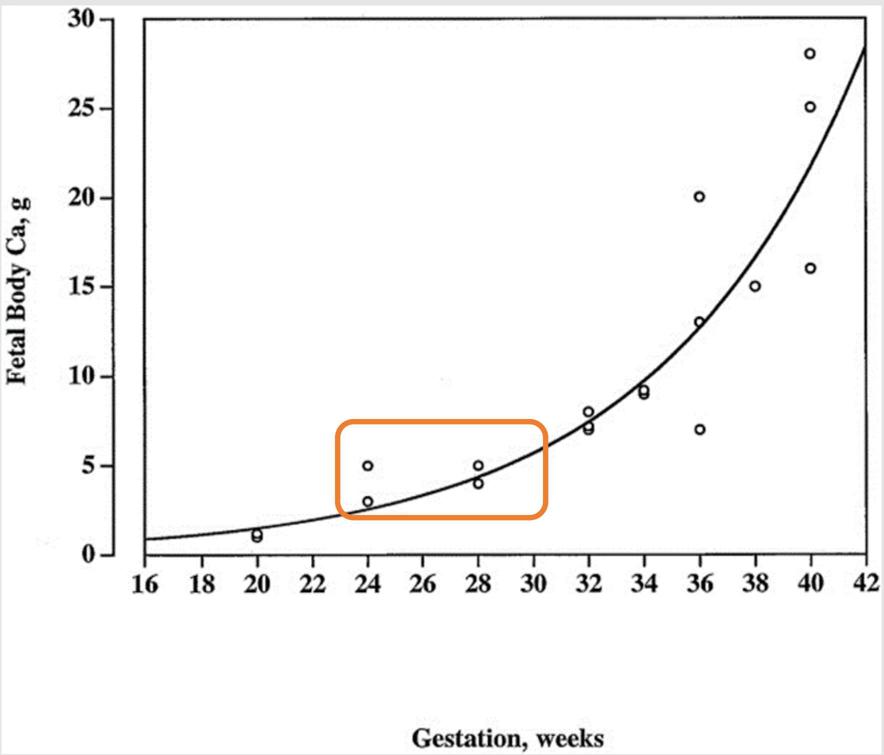
- Osteoblasts form osteoid (organic bone matrix)
- Incorporation of minerals (Ca and Phos) into newly formed osteoid

Circulation of mineral within the fetal-placental unit



- Fetus maintains higher mineral concentrations than in the mother or normal adult
- Fetal bone and mineral metabolism are critically dependent on PTH and PTH-related protein (PTHrP)

Kovacs, Physiol Rev 2014



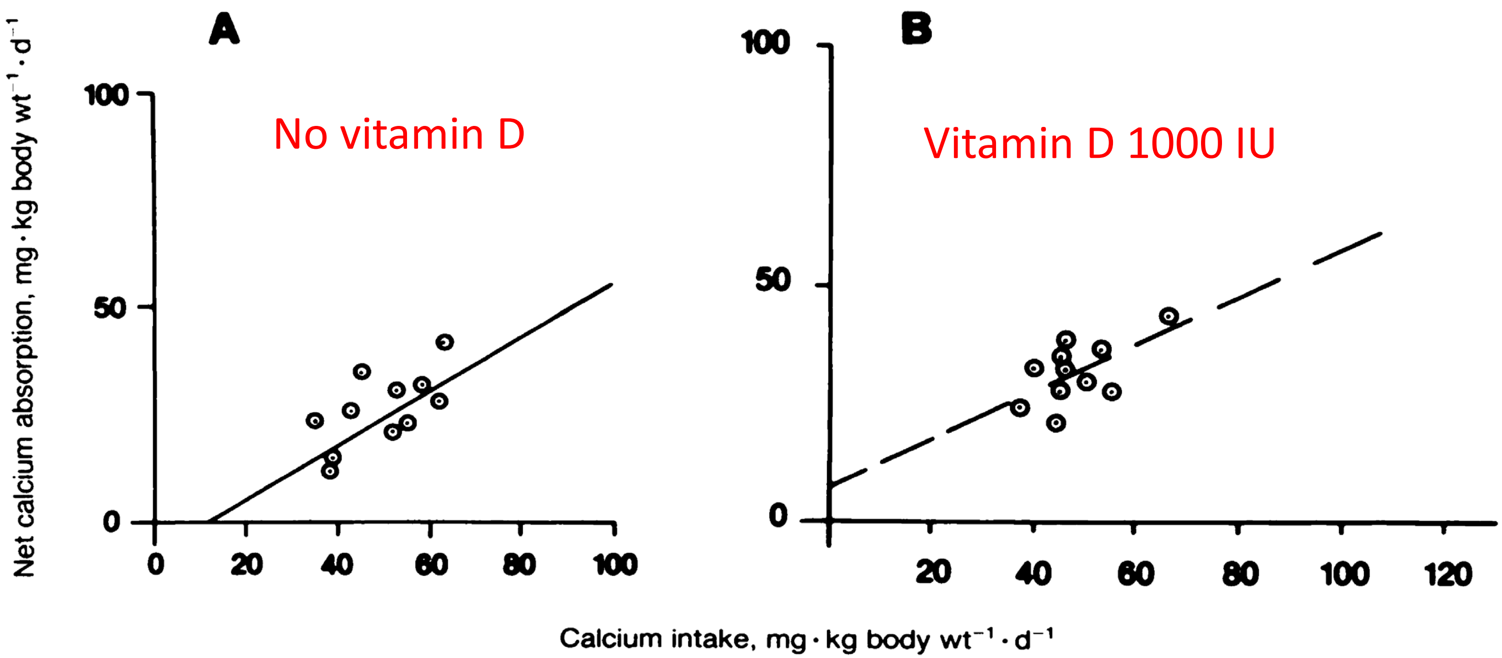
- A fetus typically accumulates 30 g of Ca by term
- 80% of mineral content is obtained in the 3rd trimester
- Ca accretion rate: 120-150 mg/kg/d
- Phos accretion rate: 75- 85 mg/kg/d

Kovacs. Physiol Rev 2014

	PLACENTAL TRANSFER
Calcium	Active transport
25 hydroxyvitamin D	Yes
1, 25 dihydroxyvitamin D_3	No
Phosphorus	Active transport
Calcitonin	No
Parathyroid hormone	No
Parathyroid hormone related peptide	No

Alshaikh et al, Nutrition in Focus. 2016

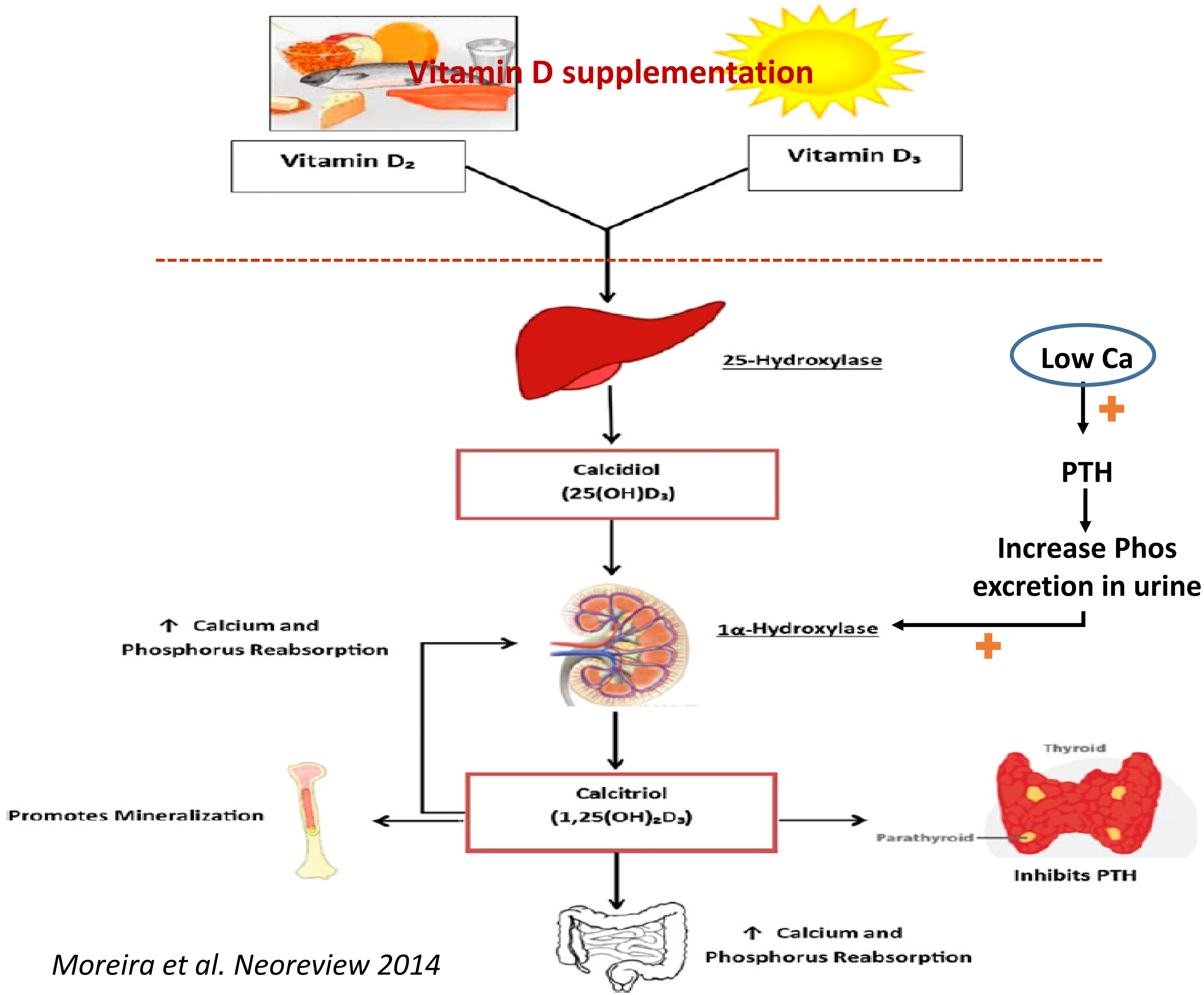
Preterm infants in the first few weeks of life



- Intestinal Ca absorption is initially a passive process facilitated by lactose
- Preventing or correcting skeletal changes of MBD can be done independent of vitamin D sufficiency

Bronner et al. Am J Clin Nutr 1992

Calcium and phosphorus hemostasis



Moreira et al. Neoreview 2014

Definition, etiology, consequences and risk factors

MBD

- MBD: Under-mineralization of the preterm infant's skeletal

- The literature uses various terminology:
  - Osteopenia of prematurity: reduction in bone mass in the absence of a skeletal mineralization disorder per se
  - Rickets of prematurity: mineralization disorders arising from lack of sufficient PO4 and/or Ca (which may be vitamin D deficiency-mediated) to mineralize the growth plate (rickets, children) and bone tissue (osteomalacia, adult)

Etiology

What is the etiology for MBD in preterm infants?

- Mainly vitamin D deficiency
- Mainly Phos deficiency
- Mainly Ca deficiency
- Phos and/or Ca deficiency→ Vit D deficiency
- Vitamin D deficiency → Ca and/or phos deficiency

Incidence and Consequences

- **Incidence** remains unknown due to lack of consensus on definition (10-32% of VLBW infants)
- **Fractures:** Can go unrecognized
  - All preterm infant: 1.8% fractures, mostly posterior rib fractures *(Lucas-Herald, pediatrics 2012)*
  - ELBW: 31% has MBD & 10% fractures *(Viswanathan 2014)*
  - 30% rib fractures *(Koo 1989)*
- Rachitic **Respiratory Distress** *(Glasgow 1977)*
- **Dolicocephaly** *(Pohlandt 1994)*
- **Long term outcomes**:
  - Low BMD and BMC at 3 years *(Mihatsch 2021)*
  - Stunning linear growth: Correlation between high ALP and height at 18 month and adulthood *(Lucas 1989, Fewtrell 2000, Abrams 1989)*

Risk factors

Risk factor	Underlying mechanism(s)
Prematurity	► Loss of maximal in utero mineralisation.
Low birth weight	► Associated with prematurity. ► Associated with placental insufficiency resulting in reduced active placental transport of minerals in utero.
Loss of maternal oestrogen	► Increased osteoclast formation and bone resorption.
Reduced physical activity	► Increased bone resorption from reduced mechanical stimulation and deformation.
Parenteral nutrition	► Limitations in calcium and phosphate content due to precipitation.
Glucocorticoids	► Reduce gut absorption of minerals. ► Direct effect on bone (increased bone resorption and reduced bone formation).
Antacids	► Reduced gut absorption of calcium (neutralisation of stomach acid).
Loop diuretics	► Increased renal calcium loss (inhibition of calcium reabsorption).
Chronic lung disease/ bronchopulmonary dysplasia	► Higher energy requirements compromising mineral supply to the bones. ► Increased use of glucocorticoids and loop diuretics.
Necrotising enterocolitis	► Prolonged periods of parenteral nutrition. ► Poor gut function and therefore poor mineral absorption.
Excessive phosphate supplementation	► Imbalance in calcium to phosphate ratio resulting in secondary hyperparathyroidism and bone resorption.

Chinoy et al. Arch Fetal & Neonatal 2019

MBD: ALP >900 IU/L **&** phos <1.8 mmol/L
High risk for MBD: ALP >900 IU/L **OR** phos <1.8 mmol/L

	Control (N= 191)	MBD (N= 27)	P-value
Gestational age (week)	30.6 (28.9, 31.6)	29.1 (27.5, 30.1)	0.005
Birth weight (g)	1280 (1099, 1440)	921 (850, 1230)	<0.001
Days on PN (day)	8 (6, 11)	10 (7, 20)	0.045
Duration of supplementary O2	120 (19, 654)	408 (96, 888)	0.05
Late-onset sepsis, n (%)	49 (26)	13 (48)	0.03
Leukomalacia, n (%)	10 (5.2)	5 (19)	0.03
Blood transfusion, n (%)	76 (40)	20 (74)	0.002

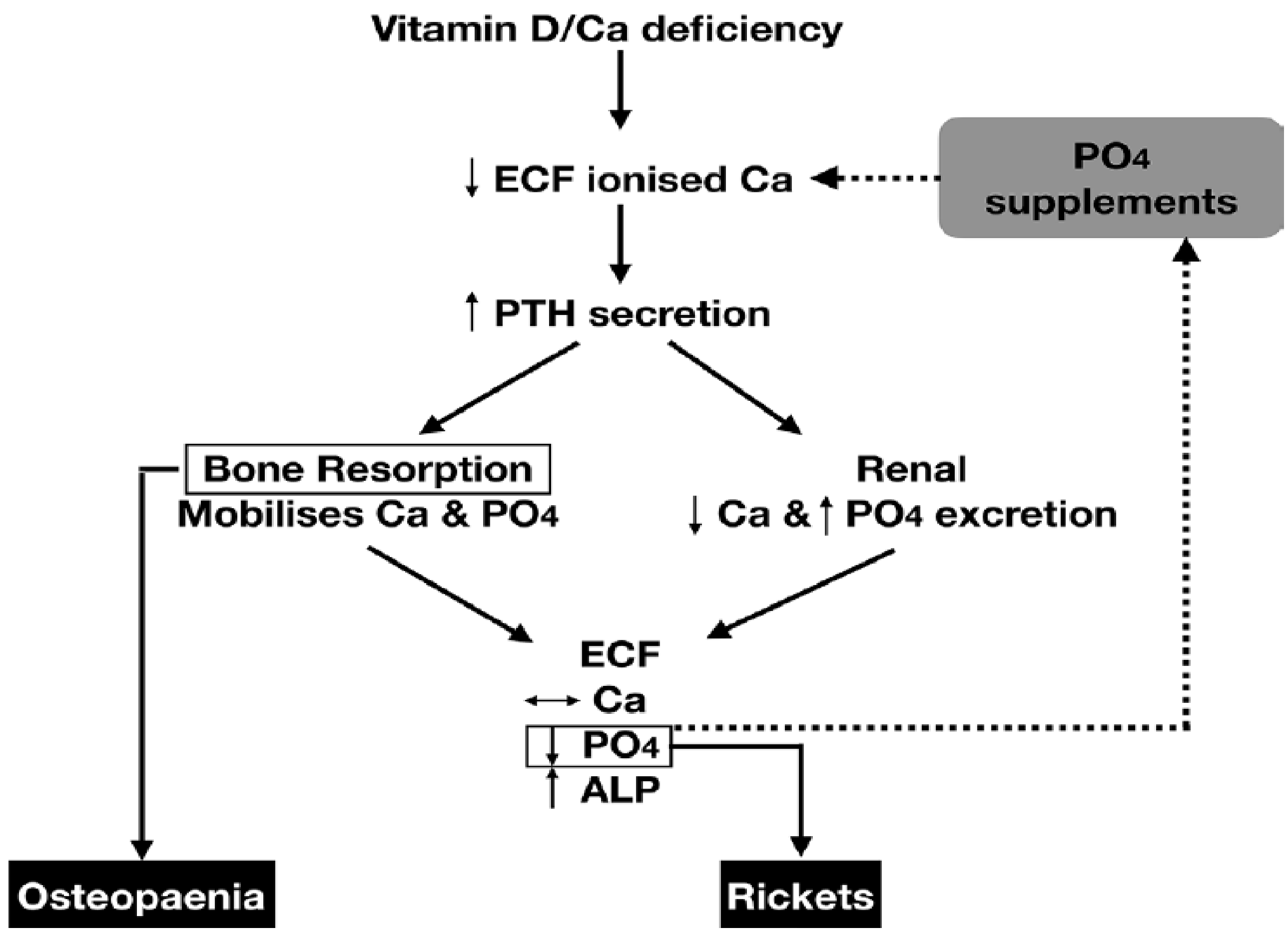
MBD: BW was the only independent risk factor aOR/100 g= 0.81 (0.66 - 0.99)
High risk for MBD:
BW aOR= 0.85 (0.73 - 0.99)
RBC transfusion aOR= 2.7 (1.3 – 5.5)

Avila-Alvarez et al. Nutrient 2020

Drug	Mechanism
Corticosteroids[16,67]	Inhibits osteoblast activity; ↑osteoclast activity ↑ excretion of Ca ↑ bone resorption/↓ formation
Loop diuretics[16,67]	↑ excretion of Ca → ↑ bone resorption
CYP P450 3A4 inducers (eg, Phenobarbital)[97,101]	↑ metabolism of vitamin D→ ↓ levels ↑ bone resorption/↓ formation
TPN[16,67]	
Suboptimal Ca/P	↑ bone resorption/↓ formation
Aluminum content	↓ formation
Emulsified mineral oil[95]	↓ absorption of vitamin D/Ca/P
Heparin[98,102,103]	↑ bone resorption/↓ formation
with prolonged therapy (more than 6 months)	
with higher dose therapy (more than 15 000 units)	
Theophylline/caffeine[96,99]	↑ excretion of Ca → ↑ bone resorption
Proton pump inhibitors[100]	↓ acid secretion→ possible ↓ Ca absorption

Begany et al, Ped Nutr Care 2012

It is important to identify the cause for high ALP



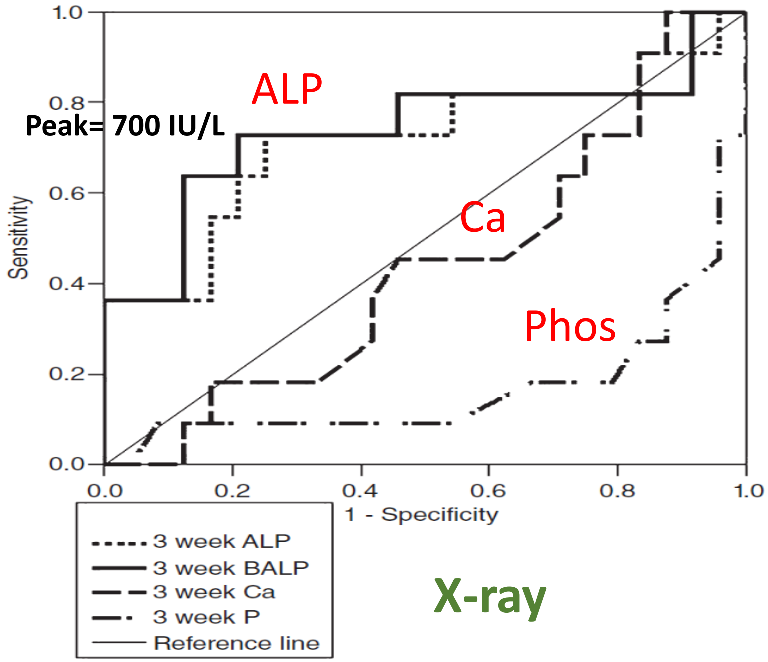
Chinoy et al. Arch Fetal & Neonatal 2019

Diagnosis

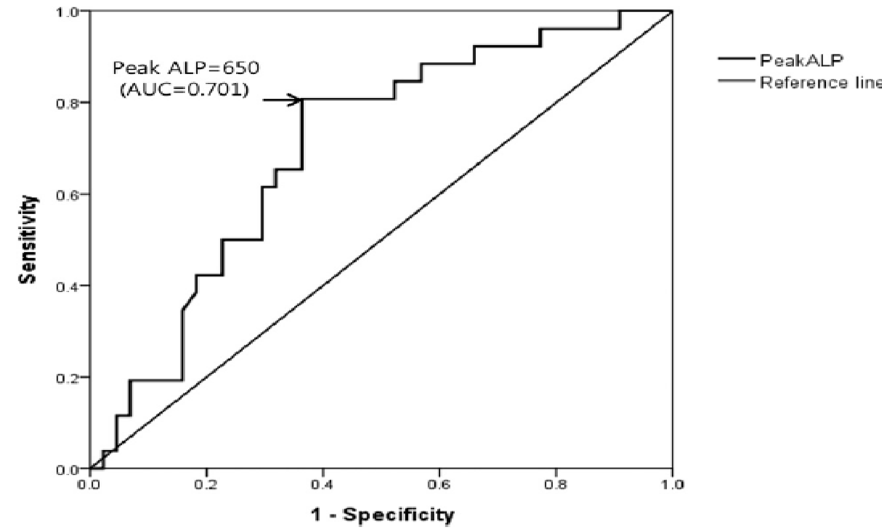
- Biochemical markers
- Urinary markers
- Radiologic test
  - Plain radiography
  - Dual-energy x-ray absorptiometry
  - Quantitative ultrasound
  - Photon absorptiometry

Biochemical & urinary markers

	Level of Interest	Key Points
ALP	>700-900 IU/L or >500 and trending up	- Elevated in liver disease - Decreased with steroids
Phos	<1.8 mmol/L <1.5 mmol/L more sensitive	- Low values correlated with MBD, esp in combo with ALP
Ca	<2.1 or >2.6 mmol/L	- Often not useful as isolated marker
PTH	>70-100 pg/mL (more sensitive > 180 pg/mL)	- Cord blood for term: 81-90 pg/ml
25(OH)D	<30 ng/mL (75 nmol/L) <20 ng/mL (50 nmol/L)= deficiency	- Similar in preterm infants with and without rickets
TRP	>95%	- Indicate inadequate phos supplement
U Ca/Cr	95^{th} centile 3.8 mmol/mmol	- Decrease with postnatal age - Low in formula-fed infant
U Phos/Cr	95^{th} centile 26.7 mmol/mmol	- Stable with postnasal age



X-ray



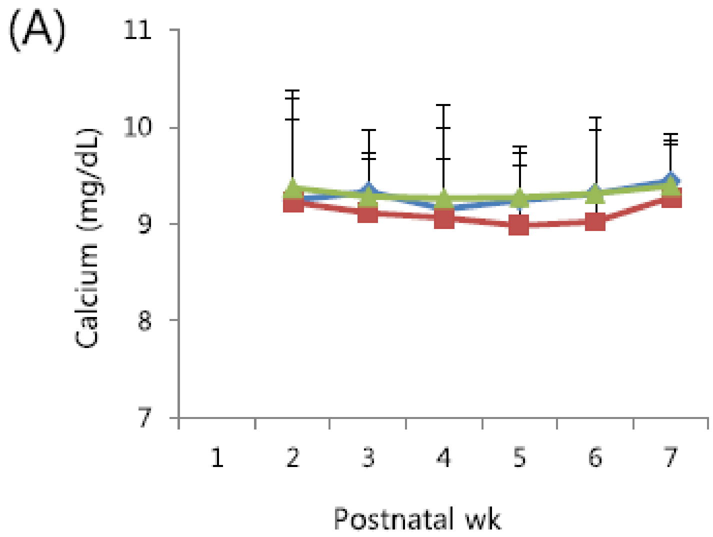
DEXA

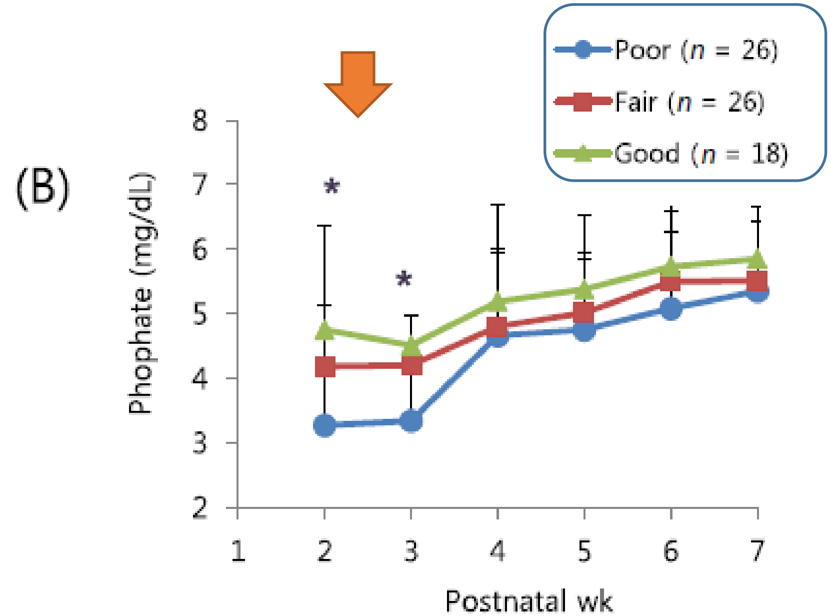
Hung et al. J Paed & child Health 2011

Lee et al. Pediatr and Neonatol 2017

ALP >900 U/L & phos <1.8 mmol/L at 3 months CGA was 100% sensitive and 71% specific for reduced BMC. **DEXA**

Backstrom et al. Acta Paediatr 2000

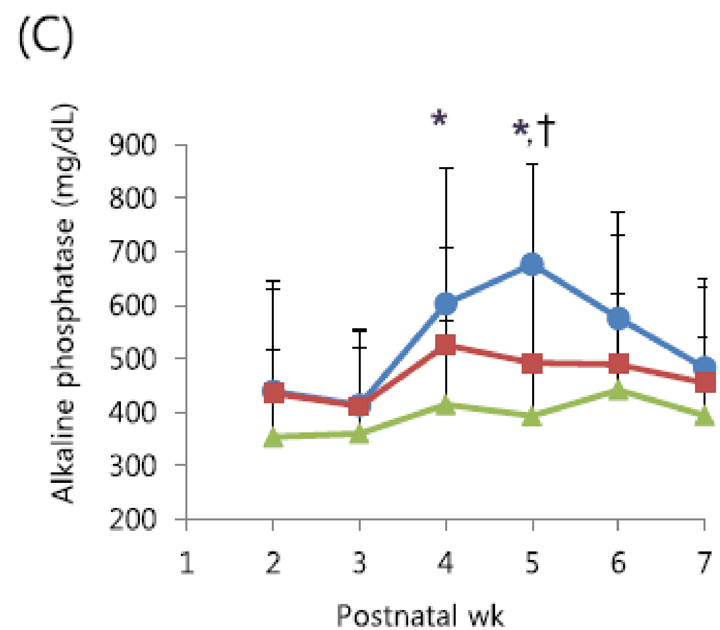




- **Measured bone mineral apparent density using DEXA**
- **Low Phos:**

  The earliest marker: 14-21 days
- **High ALP**
  - Physiologic increase in ALP in first few weeks

Lee et al. Pediatrics and Neonatology 2017



Tubular Reabsorption of Phos (TRP)

$$TRPi = \left[1 - \frac{PO_4(U) \times Cr(S)}{PO_4(S) \times Cr(U)}\right] \times 100$$

- http://www.scymed.com/en/smnxps/pshpd274.htm

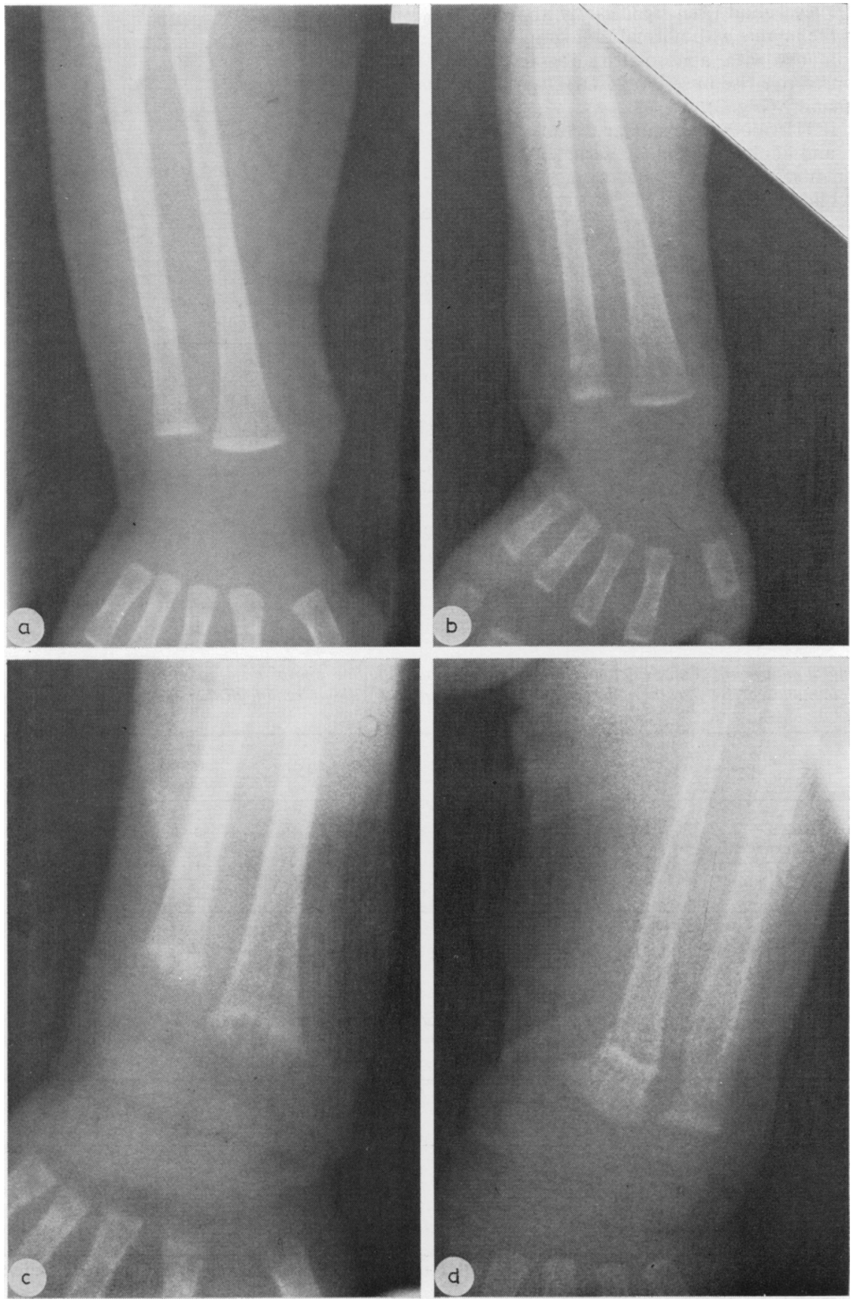
- **High TRP (>95%)**
  - Body is depleted and trying to reabsorb all the secreted phos in urine
  - If combined with **normal PTH and low serum phos** → low phos intake
- **Low TRP (<80%)**
  - Normal or primary renal injury
  - If combined with **high PTH & low/normal serum phos** → low calcium intake

- TRP ≥95% and MBD
  - Positive predictive value 17%
  - Negative predictive value 90%

Acar et al. Turk Peds Arch 2015

Radiology

Plain radiography
Dual-energy x-ray absorptiometry
Quantitative ultrasound
Photon absorptiometry

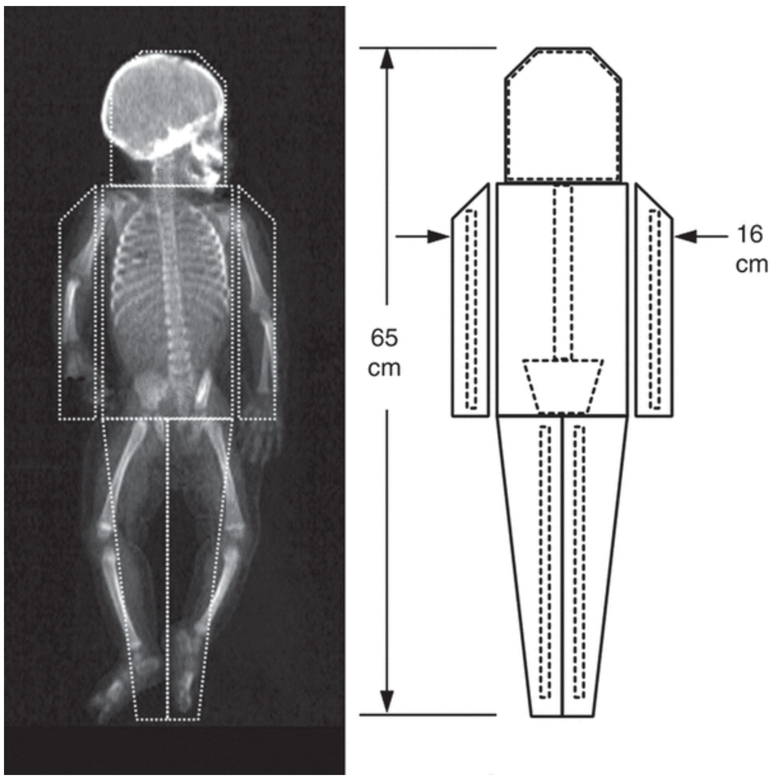


Koo classification

- 0 = normal bone
- 1= rarefaction only
- 2= bone end changes (frying/cupping metaphysis, sub-periosteal new bone formation)
- 3= fracture + above changes

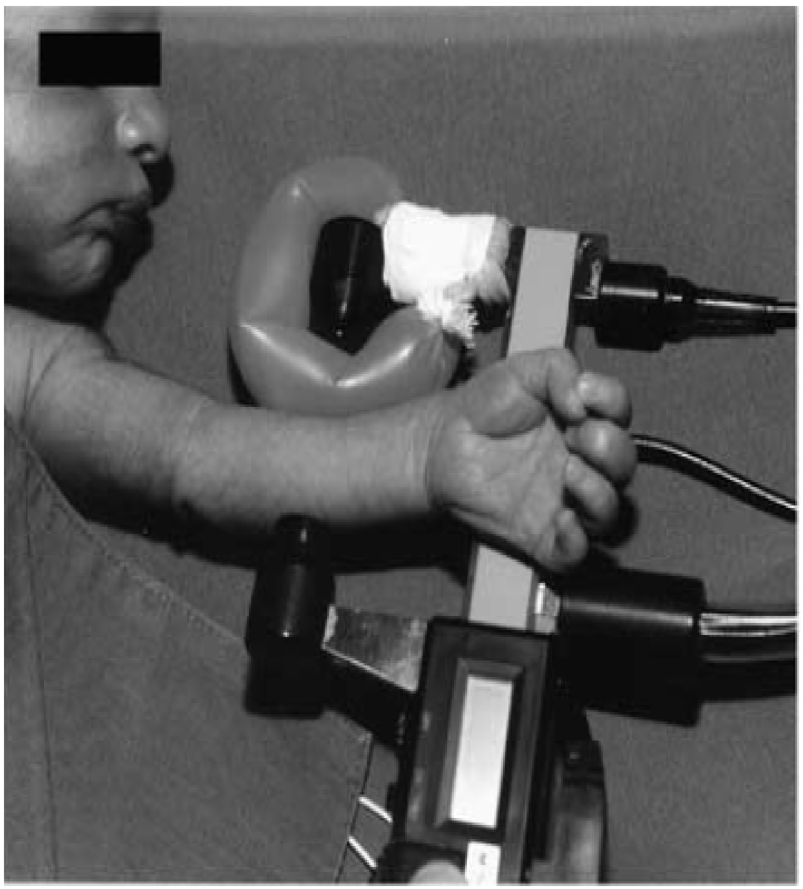
Koo et al. Arch Dis Child, 1982

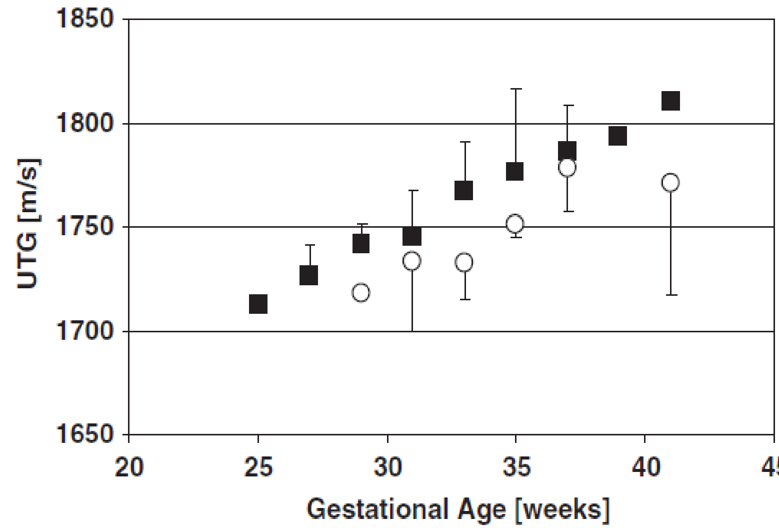
Dual-energy x-ray absorptiometry

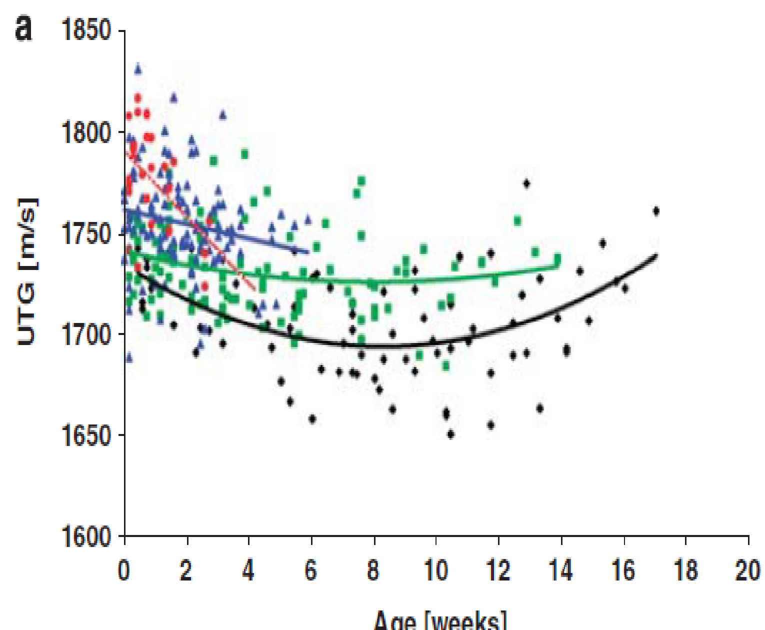


- The gold standard for research
- Difficult to perform in preterm infants
- Bone mineral content (BMC g)
- Bone mineral density (BMD g/cm2)

Quantitative US







Screening Practices

What are the preliminary MBD screening tests you order (at the first screen)? Please click all that applies.

- Calcium
- Phos
- ALP
- PTH
- 25 OH vitamin D
- TRP: Renal tubular reabsorption of phos

What are MBD screening tests you order to monitor progression? Please click all that applies.

- Calcium
- Phos
- ALP
- PTH
- 25 OH vitamin D
- TRP: Renal tubular reabsorption of phos
- X-ray
- Urine Ca/Cr ratio
- Urine Phos/Cr ratio

- There is wide variation between clinicians

Frequency of preliminary MBD screening tests (Responders= 177)

Screening Test	% Responders (n)
Serum calcium	88.1 (156)
Serum phosphate	92.7 (164)
Alkaline phosphatase	99.4 (176)
X-ray	18.1 (32)
Urine calcium or calcium:creatinine	2.8 (5)
25-(OH) vitamin D	2.8 (5)
1,25-$(OH)_2$ vitamin D	2.8 (5)
Parathyroid hormone	1.7 (3)
Urine phosphorus	0.0 (0)
Other	2.3 (4)

Frequency of tests used to monitor progression (Responders= 257)

Test	% Responders (n)
Serum phosphate	74.3 (191)
Alkaline phosphatase	73.9 (190)
Serum calcium	70.8 (182)
X-ray	40.5 (104)
1,25-$(OH)_2$ vitamin D	24.1 (62)
25-(OH) vitamin D	22.2 (57)
Parathyroid hormone	10.1 (26)
Serum magnesium	9.7 (25)
Urine calcium or calcium:creatinine	7.4 (19)
Urine phosphorus	1.6 (4)
Tubular phosphate reabsorption	1.6 (4)
Other	1.6 (4)

Kelly et al, Clinical pediatrics 2014

Screening approach

Measure Na, Ca, PO4 levels 2-3 days after reaching full feed and fortification and optimize Na & Phos*

Low to Moderate Risk

- 29-32 weeks
- 1500 – 2000 grams

High Risk

- <29 weeks
- <1500 grams
- PN >2-4 weeks
- No fortification
- Fortified with AA or EH formula

Measure Ca, PO4, & ALP levels at day 22-28 of life

Normal

ALP <500 & Po4 ≥1.8 mmol/L

+/- Growth lab after 4 weeks if the baby is still in hospital

Growth lab after 2-4 weeks until 36-37 weeks unless on supplementation

ALP>700 or >500 & trending up,
Po4 <1.8 mmol/L,
or fracture

↓

Measure TRP, PTH, ± X ray ±25(OH)D**

↓

<u>Consider Ca supplementation if:</u>

- PTH >70 pg/mL
- Low serum phos with low TRP
- Bone abnormality/fracture on X-ray

<u>Optimize vitamin D</u>

<u>Consider phosphate supplementation if</u>:

- Normal or low PTH
- Low serum phos with ≥ 95%TRP
- Bone abnormality/fracture on X-ray

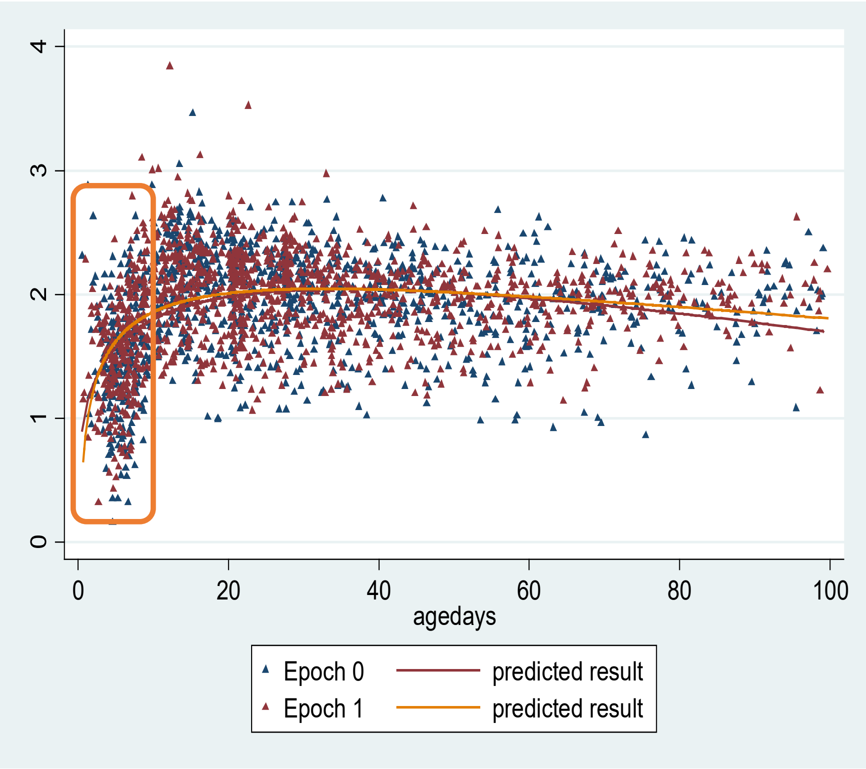
<u>Optimize vitamin D</u>

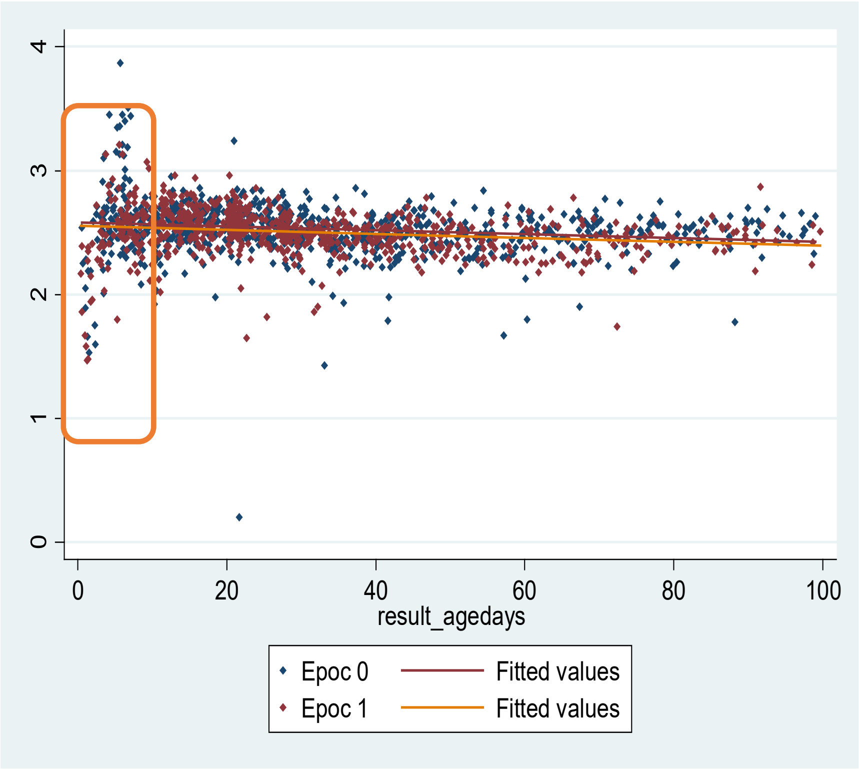
Prevention of MBD

- Micro and Macronutrients
    - Ca, Phos & Vit D:
        - Parenteral nutrition
        - Enteral nutrition
- Physical exercise program
- Review medications
- Special handling precautions

Parenteral nutrition

- Micronutrients
  - Ca, P, Mg
  - Vitamin D

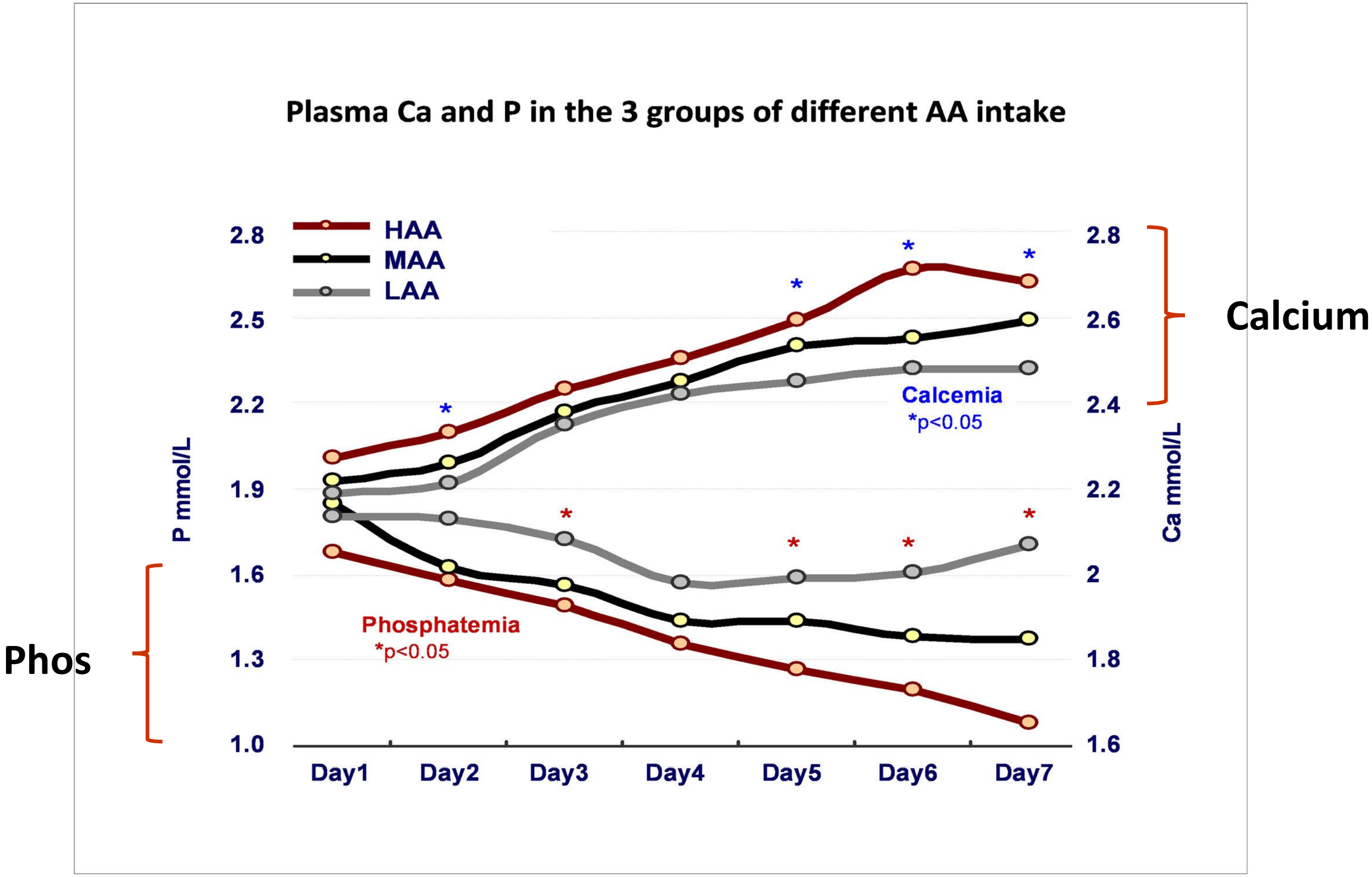




Phosphorus

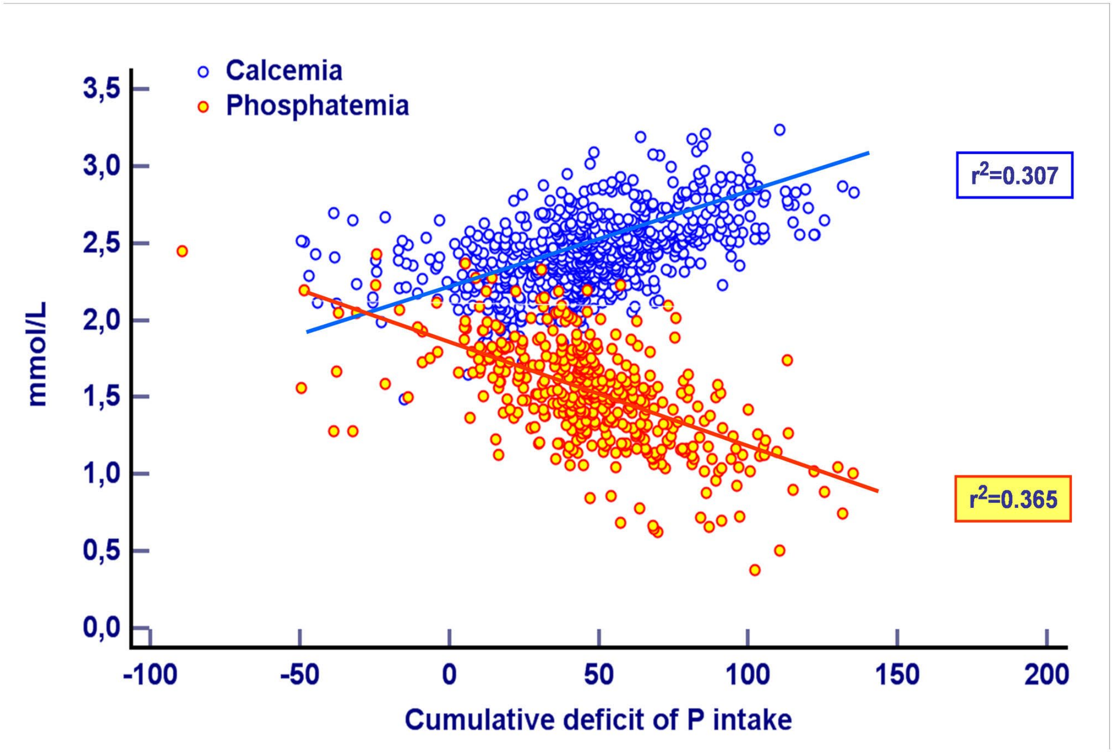
Calcium

Alshaikh et *al. 2018*



- Protein is a major determinant of tissue accretion
- 1 g/kg/d protein accretion needs 0.3 mmol/kg/d Phos

Bosante et al. BLOS 2013



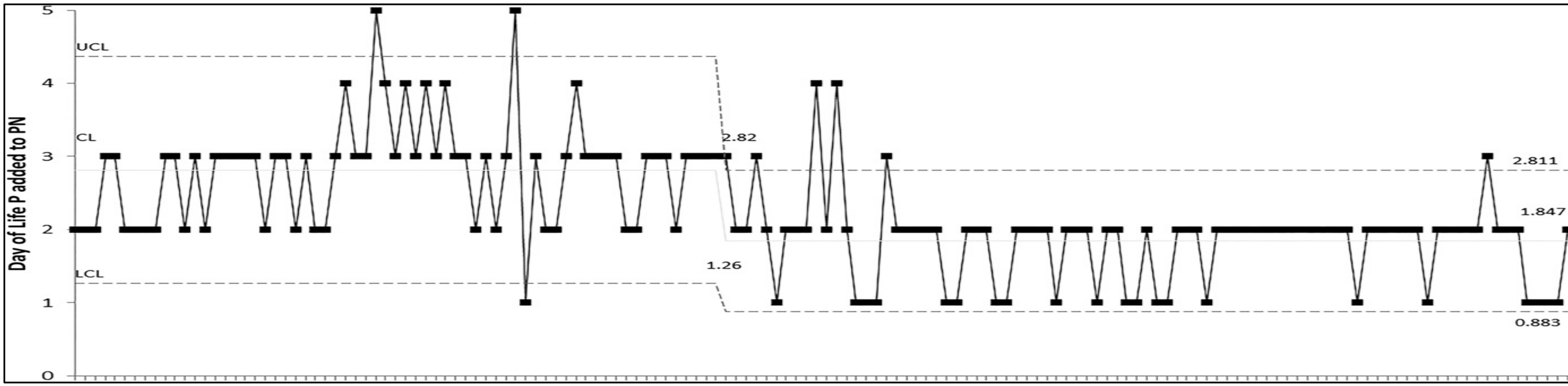
- **Phos deficiency** → ↓ATP & 2,3 DPG → left shift of O2-Hg dissociation curve → ↓peripheral O2 uptake and transport
- **Severe P deficiency**:
  - Delay weaning from respiratory support
  - Glucose intolerance

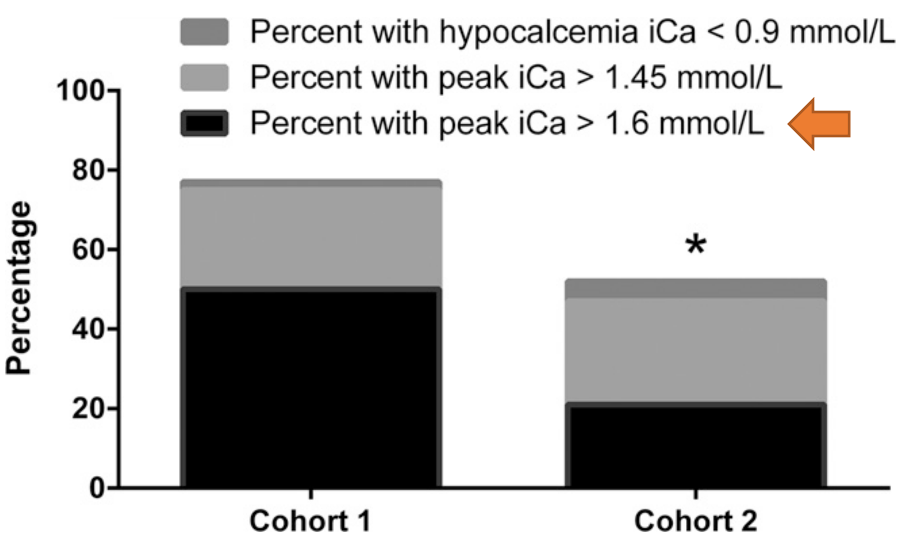
Bosante et al. BLOS 2013
Alsumrain et al. Ann Clin Lab Sci 2010
Paula et al. Horm Metab Res 1998

Age	Suggested parenteral intake in mmol (mg)/kg/d		
	Ca	P	Mg
Preterm infants during the first days of life	0.8–2.0 (32–80)	1.0–2.0 (31–62)	0.1–0.2 (2.5–5.0)
Growing premature infants	1.6–3.5 (64–140)	1.6–3.5 (50–108)	0.2–0.3 (5.0–7.5)
0–6 m[a]	0.8–1.5 (30–60)	0.7–1.3 (20–40)	0.1–0.2 (2.4–5)

- **Early PN**: Ca:P molar ratio= 0.8-1.0 → reduce hypercalcemia and hypophosphatemia
- **Late PN**: should be based on growth velocity to maintain Ca:P molar ratio= 1.3
- Organic P is recommended to prevent precipitation
- Plasma P should be monitored closely in **SGA** preterm infants
- Maternal **MgSO4** → measurement of postnatal blood levels

Mihatsch et al. ESPGHAN/ESPEN. Clinical Nutrition 2018
Wang et al. Ped & Neonatol 2020





Is it doable?

Early provision of Phos in PN may decrease incidence of hypercalcemia

Hair et al. J nutrition 2016

Enteral Nutrition

Enteral Nutrition

TABLE 4 Recommendations for Enteral Nutrition for VLBW Infants

	Calcium, mg/kg per day	Phosphorus, mg/kg per day	Vitamin D, IU/day
Tsang et al (2005)[32]	100–220	60–140	150–400[a]
Klein (2002)[33]	150–220	100–130	135–338[b]
Agostoni[c] (2010)[5]	120–140	65–90	800–1000
This AAP clinical report	150–220	75–140	200–400

[a] Text says "aim to deliver 400 IU/daily."
[b] 90–125 IU/kg (total amount shown is for 1.5-kg infant).
[c] Reflects European recommendations.

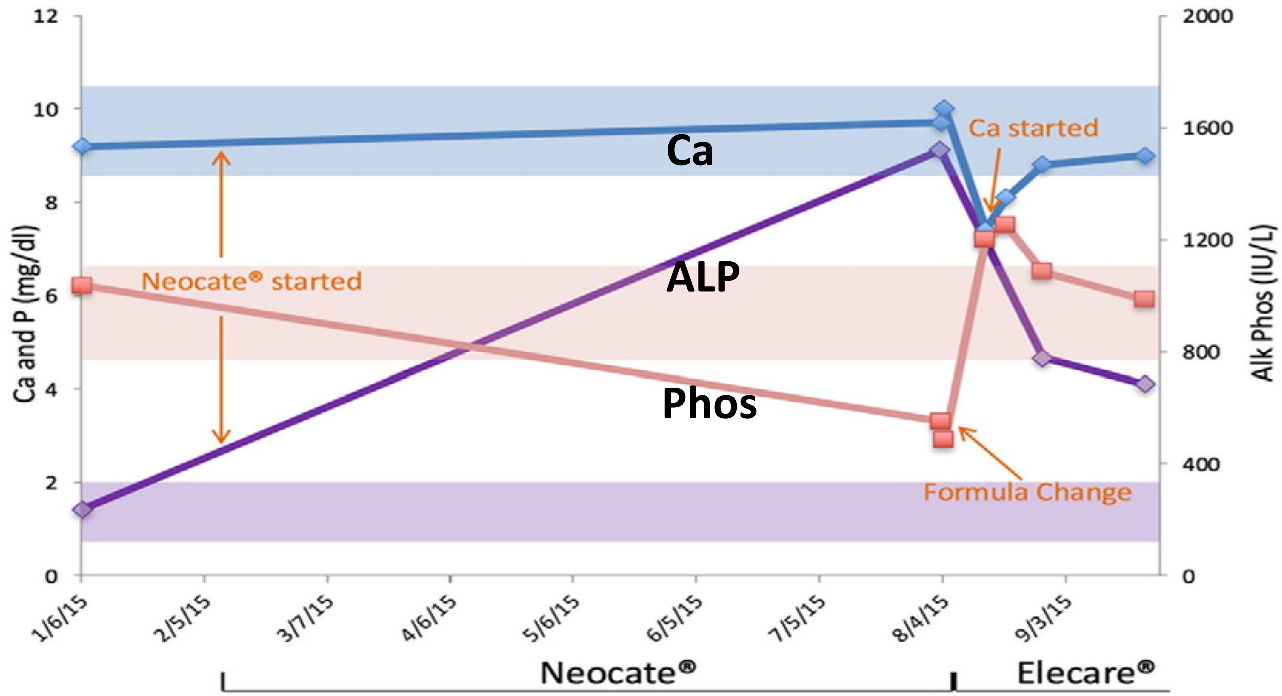
Abrams. AAP Clinical Report 2013

Enteral Feed	Ca Intake (mmol/kg/d) at 150 ml/kg/d feed	Phos Intake (mmol/kg/d) at 150 ml/kg/d feed	Vitamin D Intake (IU/kg/d)
EBM	1.05	0.75	2
EBM ± 1 Similac HMF	3.0	2.2	90
EBM ± 2 Similac HMF	4.65	3.3	180
EBM 24 ± Enfacare	1.65	1.2	15
EBM 24 ± Nutramigen	1.5	1.05	10.5
Enfamil Premature 20	4.2	2.7	243
Enfamil Premature 24	4.95	3.3	293
Enfamil Enfacare 22	3.3	2.4	78
Enfamil A+	1.95	1.35	61.5
Nutramigen 20	2.4	1.65	51
Neocate 20	3.2	3	60
Puramino 20	2.4	1.65	51

Recommended doses (AAP)

In mmol	3 – 5.5 mmol/kg/day	2.4-4.5 mmol/kg/day	200-400 IU/day*
In mg	150-220 mg/kg/day	75-140 mg/kg/day	-

Hydrolyzed and amino acid formulas



Form and source of phosphate in available amino acid formulas:

	Neocate®	Elecare®	Puramino®	Alfamino®
Form of PO4	Reformulated to K phosphate plus tribasic Ca phosphate plus Ca chloride plus Ca carbonate	Calcium phosphate plus K phosphate	Calcium phosphate plus Mg phosphate	Calcium glycerophos-phate

Ballesteros et al. PMC 2017

Vitamin D

What vitamin D dose you use for preterm infants in NICU?

- 200 IU daily
- 400 IU daily
- 800 IU daily
- 1000 IU daily
- >1000 IU daily

Vitamin D dose…

Variable	800-IU Group	400-IU Group	RR (95% CI)	*P*
40 ± 2 weeks' PMA				
n	42	45		
VDD (<20 ng/mL)	16 (38)	30 (67)	0.57 (0.37–0.88)	.008
Vitamin D severe deficiency (<5 ng/mL)	0	2 (4.4)	0.21 (0.01–4.33)	.50
3 months' CA				
n	40	40		
VDD (<20 ng/mL)	5 (12.5)	14 (35)	0.36 (0.14–0.90)	.02
Vitamin D severe deficiency (<5 ng/mL)	0	1 (2.5)	0.33 (0.01 to 7.94)	.99

800 IU daily → less vitamin D deficiency but …

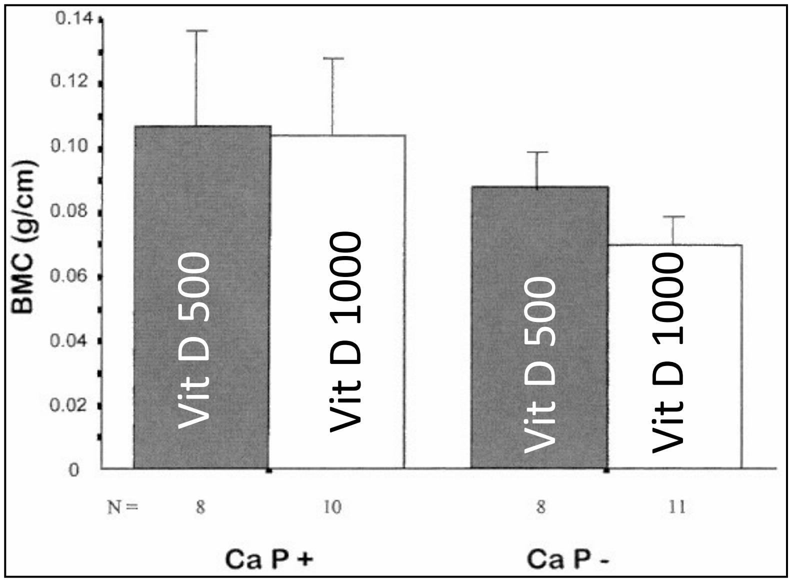
Natarajan et al. Pediatrics 2013

Variable	800-IU Group	400-IU Group	Mean Difference (95% CI)	*P*
40 ± 2 weeks' PMA				
n	42	45		
Serum calcium, mg/dL	9.9 ± 0.9	9.9 ± 0.8	−0.02 (−0.34 to 0.39)	.89
Serum phosphorus, mg/dL	6.1 ± 1.2	6.3 ± 1.1	−0.17 (−0.69 to 0.34)	.50
Serum ALP, IU/L	236 (89–572)	276 (118–556)	—	.34
Serum PTH, pg/mL	22.3 (5.5–223)	27.2 (3.8–363)	—	.23
UCa/Cr[a]	1 (0.03–6)	0.71 (0.14–5)	—	.46
UCa/Cr >0.8[a], *n* (%)	16 (64)	15 (45)	—	.16
Nephrocalcinosis, *n*	0	0	—	—
Weight, g	2489 ± 496	2468 ± 508	21 (−191 to 234)	.84
Length, cm	47.6 ± 3.3	46.6 ± 4.0	1.0 (−0.6 to 2.5)	.21
Occipitofrontal circumference, cm	33.3 ± 1.34	33.7 ± 2.4	0.4 (−0.5 to 1.2)	.36
3 months' CA				
n	40	40		
Serum calcium, mg/dL	10.1 ± 0.4	10.1 ± 0.4	0.05 (−0.14 to 0.25)	.58
Serum phosphorus, mg/dL	6.0 ± 1.1	6.2 ± 1.4	−0.24 (−0.82 to 0.34)	.42
Serum ALP, IU/L	266 (83–875)	236 (86–740)	—	.33
Serum PTH, pg/mL	27.8 (3.4–91.7)	31. 1 (4.5–135.4)	—	.48
UCa/Cr[b]	0.3 (0.08–2.3)	0.51 (0.08–2.3)	—	.27
UCa/Cr >0.8[b], *n* (%)	4 (15.4)	5 (20.8)	—	.72
Nephrocalcinosis, *n*	0	0	—	—
Weight, g	4770 ± 820	4825 ± 1053	−56 (−472 to 361)	.79
Length, cm	57.0 ± 3.4	57.8 ± 4.0	−0.8 (−2.4 to 0.9)	.35
Occipitofrontal circumference, cm	38.0 ± 1.82	38.6 ± 1.7	−0.6 (−0.2 to 1.4)	.12
BMC, g[c]	79.6 ± 16.8	84.7 ± 20.7	−5.1 (−14.1 to 4.0)	.27
BMD, g/cm^{2}[c]	0.152 ± 0.019	0.158 ± 0.021	−0.005 (−0.015 to 0.004)	.26

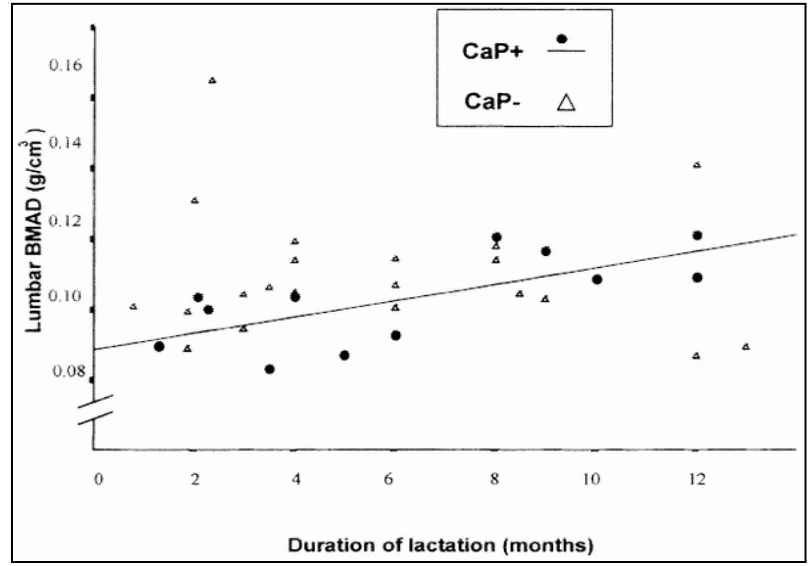
No benefits for the bones

Natarajan et al. Pediatrics 2013

3 months CGA



9-11 years



- VLBW infants on breastmilk (0-3 mo)
- Lowest BMC was in the 1000 IU group without Ca & P supplementation

Correlation between duration of lactation and lumber BMD was **significant in the Ca & P +** supplementation group only

Backstrom et al. JPGN 1999

Macronutrients

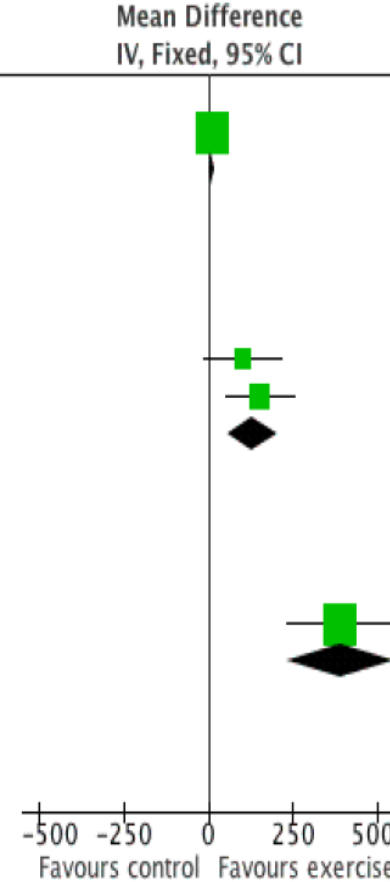
Variables	Model R^2	Model *p*-Value	B (SE)	β	*p*-Value
BMC (g) at 6 months CA, *n* = 58					
Model 1	0.394	0.021			
Constant			99.07 (103.12)		0.345
GA			−4.08 (2.77)	−0.222	0.151
Ethnicity			1.12 (2.23)	0.08	0.621
Birthweight SDS			2.65 (6.40)	0.07	0.682
Weight SDS 6 m CA			10.62 (4.06)	0.417	**0.014**
NEC			19.37 (14.78)	0.232	0.201
Mean energy intake in kcal kg^{-1} day^{-1} week 1–4			1.28 (0.57)	0.406	**0.033**
Model 2	0.337	0.013			
Constant			127.43 (101.60)		0.219
GA			−3.69 (2.77)	−0.201	0.194
Weight SDS 6 m CA			11.33 (3.86)	0.437	**0.007**
NEC			13.56 (14.26)	0.163	0.349
Mean protein intake in g kg^{-1} day^{-1} week 1–4			30.59 (24.71)	0.354	**0.046**
Model 3	0.247	0.011			
Constant			161.67 (93.78)		0.095
GA			−4.47(2.76)	−0.243	0.115
Weight SDS 6 m CA			10.78 (3.87)	0.423	**0.009**
NEC			14.15 (14.66)	0.17	0.342
Mean fat intake in g kg^{-1} day^{-1} week 1–4			22.14 (11.22)	0.343	0.05

Fat & protein intakes in the first 4 weeks are also associated with BMC & BMD at **6-month CGA**

Calor et al. Nutrients 2021

Physical activity programs

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Radial bone mineral content (mg/cm) measured by single photon absorptiometry (SPA)								
Moyer-Mileur 1995	53.3	12	12	42.7	10	11	100.0%	10.60 [1.60, 19.60]
Subtotal (95% CI)			**12**			**11**	**100.0%**	**10.60 [1.60, 19.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
1.2.2 Forearm bone mineral content (mg) measured by dual-energy x-ray absorptiometry (DEXA)								
Moyer-Mileur 2000	763	145	16	660	185	16	43.0%	103.00 [-12.17, 218.17]
Moyer-Mileur 2008	765	139	22	613	138	11	57.0%	152.00 [51.88, 252.12]
Subtotal (95% CI)			**38**			**27**	**100.0%**	**130.91 [55.35, 206.47]**
Heterogeneity: $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0\%$								
Test for overall effect: Z = 3.40 (P = 0.0007)								
1.2.3 Whole body bone mineral content (mg) measured by dual-energy x-ray absorptiometry (DEXA)								
Vignochi 2008	687.5	262.3	15	298.4	167.5	14	100.0%	389.10 [229.98, 548.22]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**389.10 [229.98, 548.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.79 (P < 0.00001)								



Test for subgroup differences: $Chi^2 = 31.08$, df = 2 (P < 0.00001), $I^2 = 93.6\%$

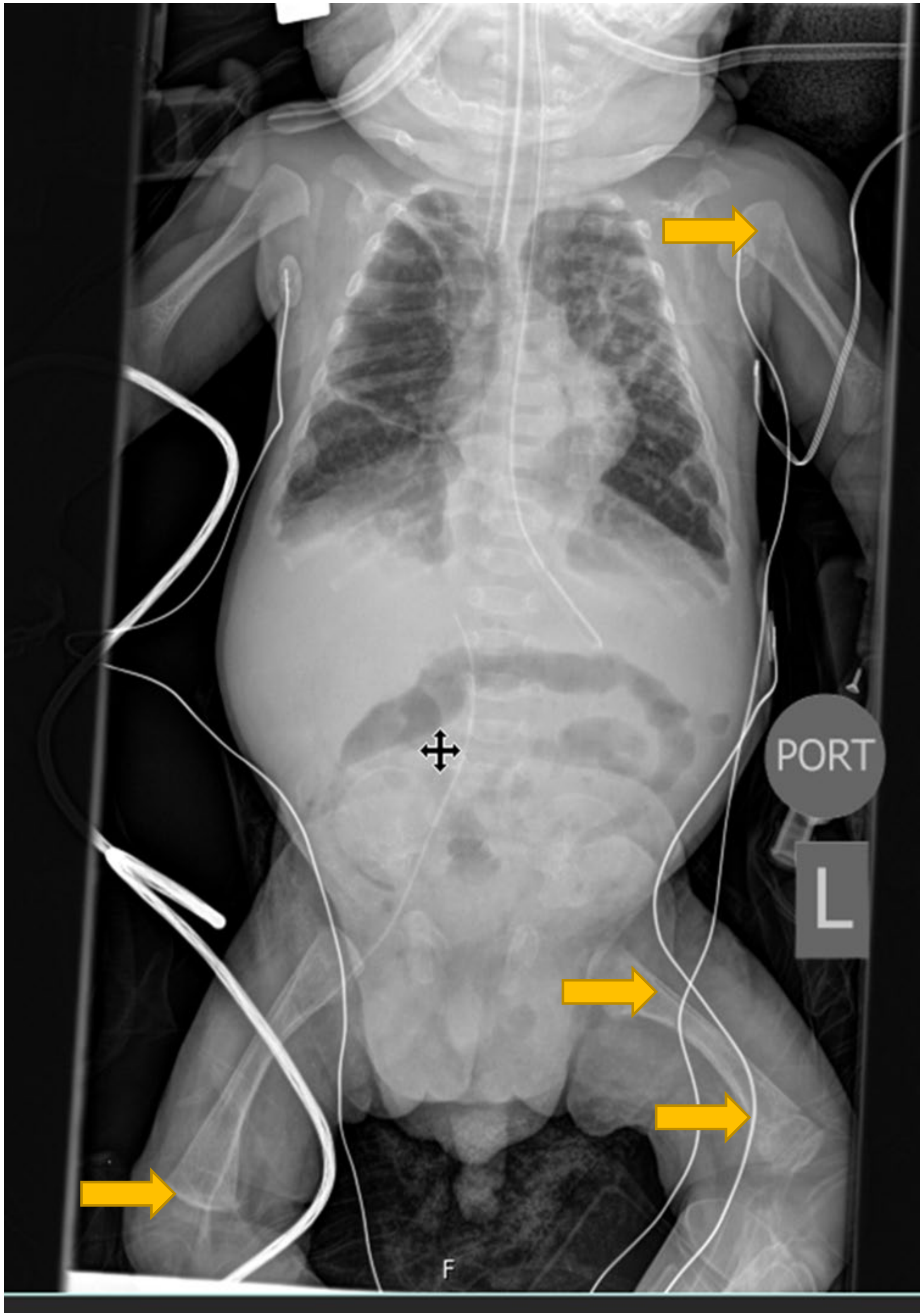
Schulzke et al. Cochrane 2014

Conclusion

- Adequate calcium and phos intake is critical to prevent MBD
- Appropriate Ca:P ratio is important and should always be maintained when supplementing calcium and phos
- Screening and early identification of MBD is critical to prevent complications
- MBD may have long term consequences
- Significant knowledge gaps exist regarding screening, prevention, and long-term sequelae

Answers

- Bone rarefaction
- Subperiosteal bone formation
- Metaphyseal alteration
- Long bone fracture



Answers

- **Etiology:** Phos and/or Ca deficiency followed by Vitamin D deficiency

- **Recommendation for vitamin D dose** for prevention of metabolic bone disease:
  - Enteral: 200–400 IU/day (AAP) to 800–1000 IU/day (ESPGHAN)
  - Don't exceed 1000 IU per day for prevention

THANK YOU

SOCIETY OF NEONATAL GASTROENTEROLOGY
NUTRITION & GROWTH

https://cumming.ucalgary.ca/research/neonatal-growth