Metabolic Bone Disease of Prematurity

Emese Erika Boros

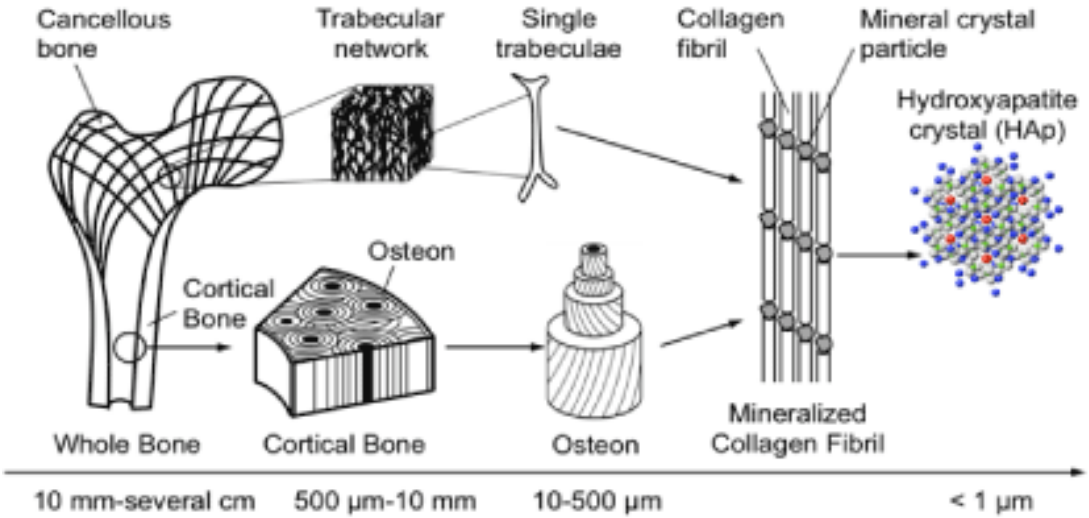
Endocrinologie pédiatrique

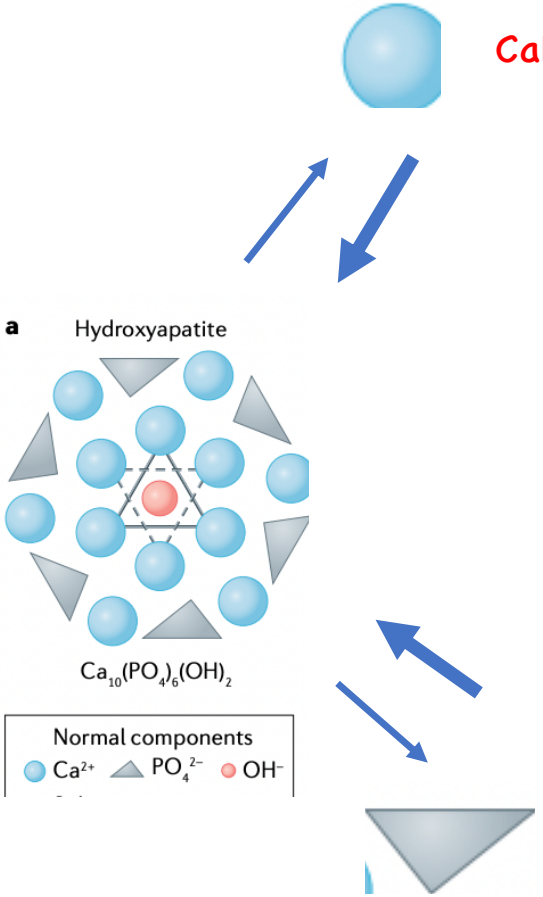
HUB-HUDERF

What about bones strength in this baby?

MBDP, E Boros

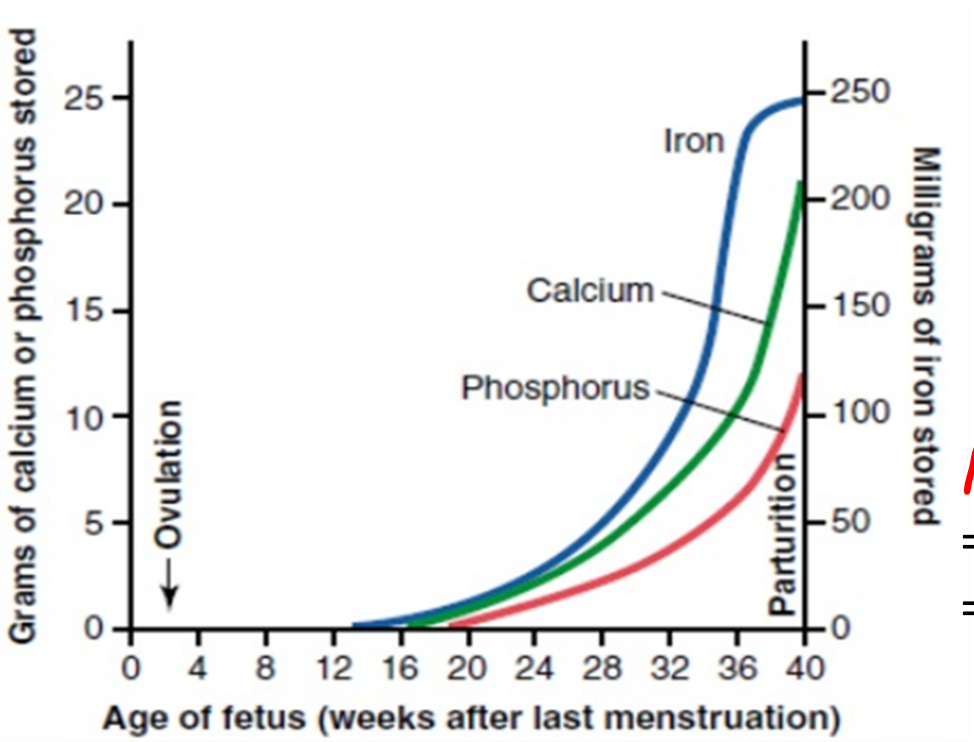
The bone





Collins M et al, 2022
Gamagedera et al

Mineral accretion during pregnancy



Preterm birth

↓

Skeletal demineralisation arised from

Inadequate provision of calcium and phosphate in utero

=

Metabolic Bone Disease of Prematurity

= Osteopenia of prematurity

= Rickets of prematurity

Why thinking about his bones?

Short term complications:

Clinical manifestation of metabolic bone disease of prematurity

- Arrested growth velocity (reduced linear growth with normal head growth)
- Features of hypocalcemia (jitteriness, tetany)
- Features of rickets
- Spontaneous fractures of ribs and long bones
- Pain while handling
- Respiratory distress
- Deranged pulmonary function
- Difficulty in weaning from ventilator

	No MBDP group N=191	**MBDP group N=27**
Duration of non invasive ventilation	96 (51, 186)	120 (60, 402)

Avila-Alvarez et al 2020

Why thinking about his bones?

- Impact of MBPD on neurodevelopment at 2 years

Bayley Scales among infants with and without metabolic bone disease at 2 years of age.

	No MBD (n = 362)	**MBD** (n = 97)	
Bayley-III Scales *	**Median (IQR)**	**Median (IQR)**	***p*-Value**
Cognitive	90.0 (85.0–95.0)	90.0 (80.0–95.0)	<0.001
Motor	94.0 (88.0–100.0)	88.0 (82.0–94.0)	<0.001
Language	94.0 (86.0–100.0)	89.0 (83.0–97.0)	0.014

Chen et al 2024

Why thinking about his bones?

Long term complications: short stature?

Neonatal factors predicting childhood height in preterm infants: Evidence for a persisting effect of early metabolic bone disease?

Mary S. Fewtrell, MD, MRCP, FRCPCH, Timothy J. Cole, PhD, Nicholas J. Bishop, MD, MRCP, FRCPCH, and Alan Lucas, MD, FRCP, FRCPCH

Prospective study of: preterm infants (birth weight <1850g)
Height measurements

- at 18 months (n = 765)
- 7.5 to 8 years (n = 772)
- 9 to 12 years of age (n = 503)

Table III. Relative influence of neonatal factors and childhood growth on height at 9 to 12 years*

Factor	Regression coefficient	t	*P* value
7.5-8 year height SD score	0.92	33.43	<.001
18 months length SD score	–0.060	–2.35	.02
Birth weight SD score	–0.057	–3.33	.001
Pubertal vs prepubertal	0.31	6.47	<.001
Peak ALP >1200 IU	–0.12	–2.14	<.03

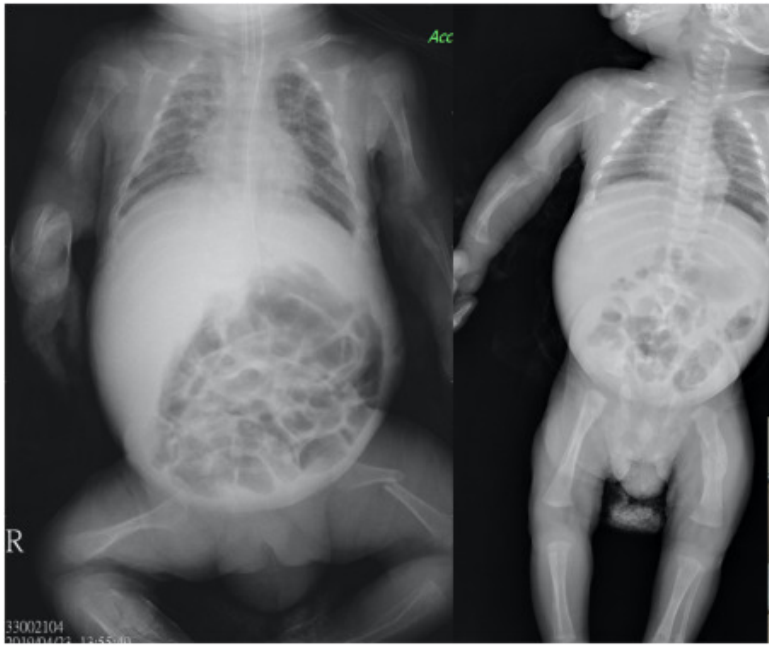
Why thinking about his bones?

- Short term complications:
  - Risk of spontaneous fractures
  - Rib fracture
  - Osteopenia

  } influence respiratory distress weakening the rib cage

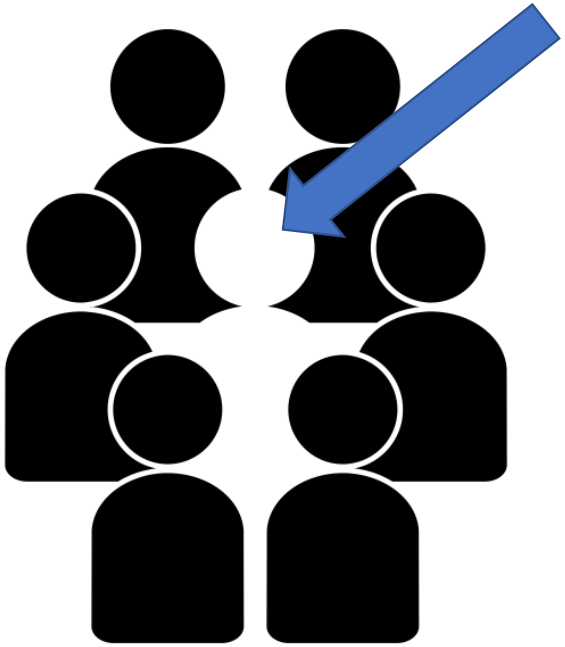
- Long term complications:
  - Final height
  - Neurodevelopment

Metabolic Bone Disease of Prematurity



Tsung-Mu Wu et al, 2023

Which preterm will be affected?



Received: 6 December 2023 | Revised: 30 April 2024 | Accepted: 3 May 2024
DOI: 10.1111/apa.17273

ACTA PÆDIATRICA WILEY

ORIGINAL ARTICLE

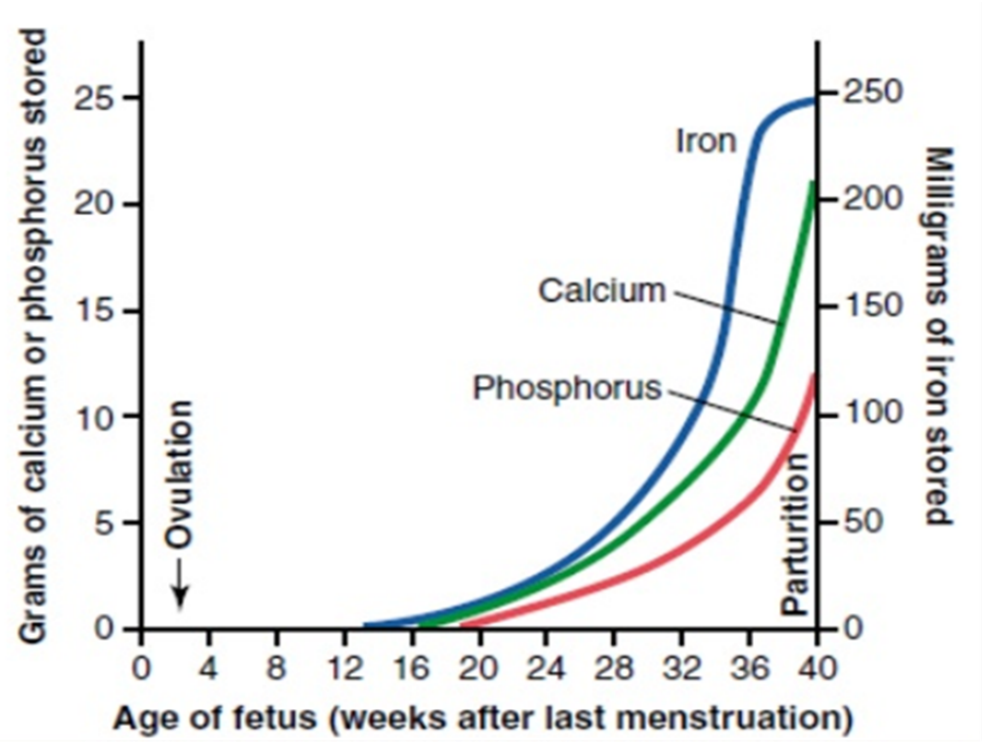
European survey showed wide variations in diagnostic procedures and management strategies for metabolic bone disease of prematurity in 22 countries

Luise Brado[1] | Daniel Matheisl[1] | Eva Mildenberger[2] | Hans Fuchs[1] | Daniel Klotz[1] | André Kidszun[3]

TABLE 2 Presumed risk factors for metabolic bone disease of prematurity, $n = 73$ units.

Risk factor		Number of units *n* (%) that reported the risk factor
Gestational age	<28 weeks GA	26 (36%)
	<30 weeks GA	11 (15%)
	<32 weeks GA	33 (45%)
Birth weight	<1000 g BW	25 (34%)
	<1250 g BW	8 (11%)
	<1500 g BW	37 (51%)
TPN	TPN > 7 days	11 (15%)
	TPN > 14 days	42 (58%)

Mineral accretion during intra-uterine life

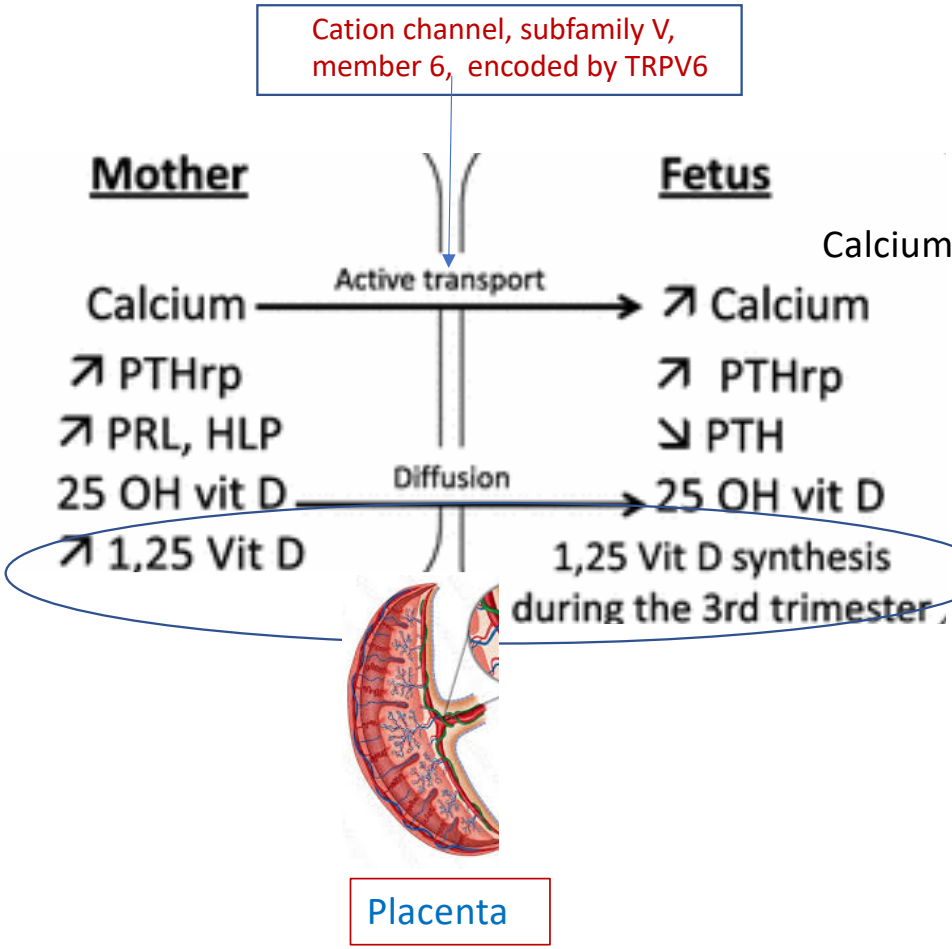


During the 3rd trimester:

- **Calcium: 100-120 mg/kg/day**
- **Phosphate: 50-65 mg/kg/day**

Rodolfo R 2016

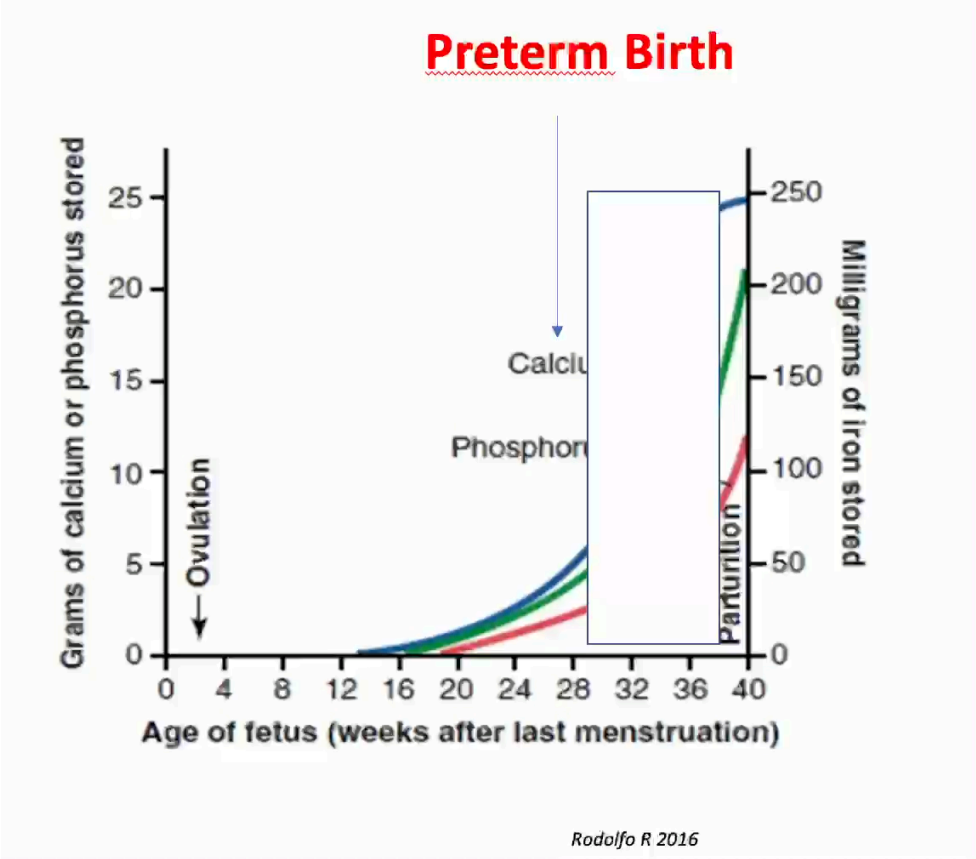
Mineral homeostasis during pregnancy

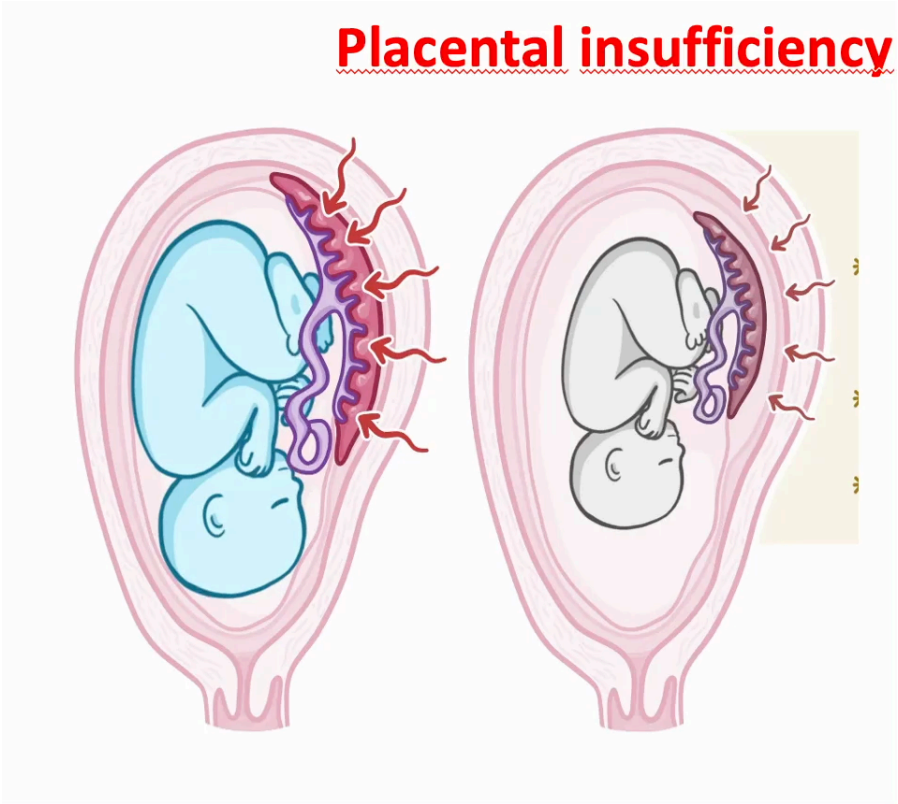


Calcium gradient 1,0 to 1,4 in fetus

Phosphate transport

Prenatal Risk Factors for MBDP





Postnatal Risk Factors for MBDP

- Calcium and Phosphate intake
  - Parenteral Nutrition (PN)
    - Standard PN ➔ Provides **60–70% of mineral requirements**
      - (Solubility constraints for optimal intake)

PN (adapted from [45, 46])	Ca[c]	PO4[d]
Preterm infants during first few days Ca:PO4 ratio 0.8–1:1	32–80 mg/kg/day (0.8–2 mmol/kg/day; 1.6–4 mEq/kg/day)	31–62 mg/kg/day; (1–2 mmol/kg/day)
Preterm infants after first few days Ca:PO4 ratio 1–1.3:1	50–80 mg/kg/day (1.25–2 mmol/kg/day; 2.5–4 mEq/kg/day)	39–93 mg/kg/day (1.25–3 mmol/kg/day but limited to 1.5–2 due to solubility)

During the 3rd trimester:
- **Calcium: 100-120 mg/kg/day**
- **Phosphate: 50-65 mg/kg/day**

The recommended parenteral intake for calcium, phosphorus, and magnesium intake in newborns and children on parenteral as follows (LoE 2, 3 and 4, RG 0, conditional recommendation)

Age	Ca mmol (mg)/kg/d	P mmol (mg)/kg/d
Preterm infants during the first days of life	0.8–2.0 (32–80)	1.0–2.0 (31–62)
Growing Premature	1.6–3.5 (64–140)	1.6–3.5 (50–108)
0–6 m*	0.8–1.5 (30–60)	0.7–1.3 (20–40)

Grover et al 2024
Espaghn recommandation 2018

Postnatal Risk Factors for MBDP

- Calcium and Phosphate intake
  - Enteral Intake
    - Unfortified Breast Milk or infant formula → Insufficient Ca and PO4 intake for preterm infants
    - Preterm Infant Formula → Higher Ca and PO4 content, but **variable bioavailability**
    - Human Milk Fortifiers → Additional Ca and PO4 intake, but **variable tolerance**

Enteral nutrition	Ca, mg/kg/day	PO4, mg/kg/day
2013 AAP Clinical Report Recommendations [14]	150–220	75–140
Ca, PO4, and vitamin D content in human milk and commonly used formulas[a]		
Unfortified human milk (20 kcal/oz)[b] Ca:PO4 ratio 2:1	45	22
Fortified human milk (24 kcal/oz)[b] Ca:PO4 ratio 1.7:1	200	115
Preterm formula (24 kcal/oz) Ca:PO4 ratio 1.8:1	220	120
Transitional formula (22 kcal/oz) Ca:PO4 ratio 1.8:1	138	75

Grover et al 2024

Postnatal Risk Factors for MBDP

- Medications Affecting Mineral Homeostasis

Medications	
Glucocorticoids	Increase bone resorption Reduce bone formation
Loop diuretics (furosemide)	Induce hypercalciuria
CYP450 3A4 inducers (phenobarbital)	Induce vitamin D metabolism
Methylxanthines (theophylline/caffeine)	Increase bone resorption
Anticoagulants	Reduce bone formation
Aluminum content in PN, including parenteral Ca and PO4 supplements	Reduce bone formation

Grover et al 2024

Risk factors for MBDP

RESEARCH ARTICLE

Risk factors for metabolic bone disease of prematurity: A meta-analysis

Jie Wang[1‡], Qian Zhao[1‡], Baochang Chen[1], Jingfei Sun[2], Jiayu Huang[1], Jinfeng Meng[1], Shangbin Li[1], Weichen Yan[1], Changjun Ren[1*], Ling Hao[1*]

1 The First Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China, **2** People's Hospital of Zhengding County, Shijiazhuang, Hebei Province, China

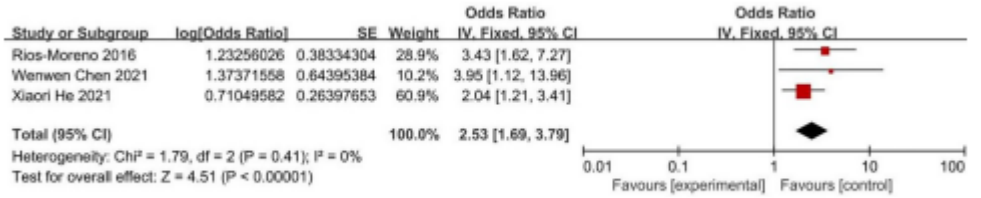


Fig 6. Forest diagram of the relationship between septicemia and the incidence of MBDP.

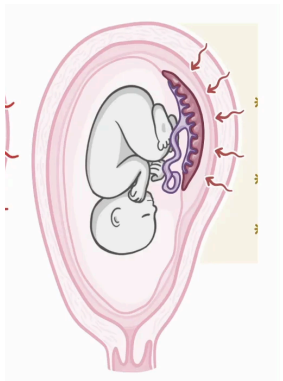
Conclusion:

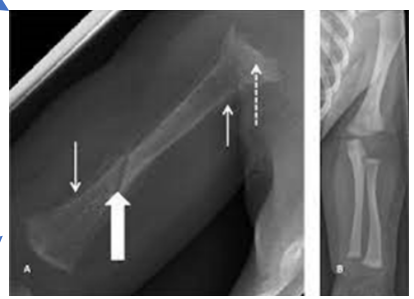
Factors that may increase the risk of MBDP:

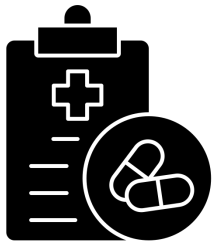
- Birth weight <1000g
- Gestational age <32 weeks
- Parenteral nutrition time
- Intrauterine growth retardation
- Septicemia

Metabolic Bone Disease of Prematurity

- multifactorial
- arises from
  - Inadequate provision of calcium and phosphate in utero+/- after birth
  - Increased bone resorption +/- reduced bone formation after birth







www.efcni.org; www.cpbf-fbpc.org ; www.elhee.com

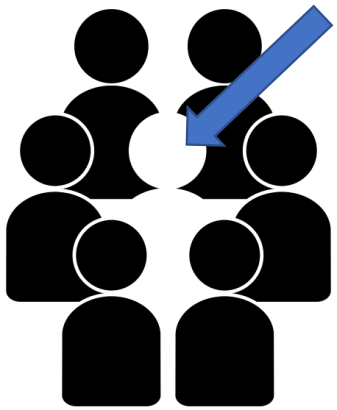
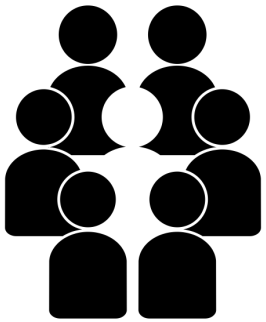


Table 1. Risk factors for development of MBDP

Risk factor	Mechanism
At birth	
Prematurity (< 32 weeks' gestation)	Lack of in utero mineralization
Extremely (<1,000 g) and very (<1,500 g) low birth weight	Reduced placental transfer of minerals in utero
Postnatal	
PN (>4–5 weeks' duration)	Limits Ca and PO4 supplementation
Necrotizing enterocolitis	Prolonged PN Poor gut function
Chronic lung disease	High energy requirements Fluid restriction Need for glucocorticoids and loop diuretics
Septicemia	
Medications	
Glucocorticoids	Increase bone resorption Reduce bone formation
Loop diuretics (furosemide)	Induce hypercalciuria
CYP450 3A4 inducers (phenobarbital)	Induce vitamin D metabolism
Methylxanthines (theophylline/caffeine)	Increase bone resorption
Anticoagulants	Reduce bone formation
Aluminum content in PN, including parenteral Ca and PO4 supplements	Reduce bone formation

Adapted from Grover et al 2024, Chinoy et al 2019 and Wang et al 2022



Initial goal:

Prevention of **M**etabolic **B**one **D**isease of **P**rematurity

The recommended parenteral intake for calcium, phosphorus, and magnesium intake in newborns and children on parenteral nutrition in mmol (mg)/kg/d is as follows (LoE 2, 3 and 4, RG 0, conditional recommendation)

Age	Ca mmol (mg)/kg/d	P mmol (mg)/kg/d	Mg mmol (mg)/kg/d
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	1.6–3.5 (64–140)	1.6–3.5 (50–108)	0.2–0.3 (5.0–7.5) infants
0–6 m*	0.8–1.5 (30–60)	0.7–1.3 (20–40)	0.1–0.2 (2.4–5)
7–12 m	0.5 (20)	0.5 (15)	0.15 (4)
1–18 y	0.25–0.4 (10–16)	0.2–0.7 (6–22)	0.1 (2.4)

Mihatsch et al, 2018, ESPGHAN recmmandation

Initial goal

Prevention of Metabolic Bone Disease of Prematurity

Enteral nutrition	Ca, mg/kg/day	PO4, mg/kg/day
2013 AAP Clinical Report Recommendations [14]	150–220	75–140
Ca, PO4, and vitamin D content in human milk and commonly used formulas[a]		
Unfortified human milk (20 kcal/oz)[b] Ca:PO4 ratio 2:1	45	22
→ Fortified human milk (24 kcal/oz)[b] Ca:PO4 ratio 1.7:1	200	115
→ Preterm formula (24 kcal/oz) Ca:PO4 ratio 1.8:1	220	120
Transitional formula (22 kcal/oz) Ca:PO4 ratio 1.8:1	138	75

Is prevention enough?

ORIGINAL ARTICLE: HEPATOLOGY AND NUTRITION

Early High Calcium and Phosphorus Intake by Parenteral Nutrition Prevents Short-term Bone Strength Decline in Preterm Infants

*L. Pereira-da-Silva, †A.B. Costa, †L. Pereira, †A.F. Filipe, *D. Virella, *E. Leal, †A.C. Moreira, ‡M.L. Rosa, †L. Mendes, and *M. Serelha

- 46 infants with low intake
- 40 infants with high intake

Bone strength measurements with speeed of sound (ultrasound)

Conclusions: Early assigned parenteral intake of Ca 75 $mg \cdot kg^{-1} \cdot day^{-1}$ and P 44 $mg \cdot kg^{-1} \cdot day^{-1}$ significantly contributed to preventing short-term bone strength decline in preterm infants.

Is prevention enough?

BMJ Open Quality

Early calcium and phosphorus supplementation in VLBW infants to reduce metabolic bone disease of prematurity: a quality improvement initiative

MV Krithika ,[1,2] Umamaheswari Balakrishnan,[1] Prakash Amboiram ,[1] Mohammed Shafi Jan Shaik,[1] Ashok Chandrasekaran,[1,3] Binu Ninan[1,4]

Conclusion Implementation of QI initiatives decreased the MBD rate from 35% to <20%. Early parenteral calcium and phosphorus supplementation in TPN and optimising enteral supplementation with multicomponent fortifiers appear to have significant reduction in the incidence of MBD.

2022

Is prevention enough?

Effect of early preventive supplementation with calcium and phosphorus on metabolic bone disease in premature infants

Xuejing Xu[1], Hongfang Ma[1], Shuqi Cheng[1] and Jiang Xue[1,2*]

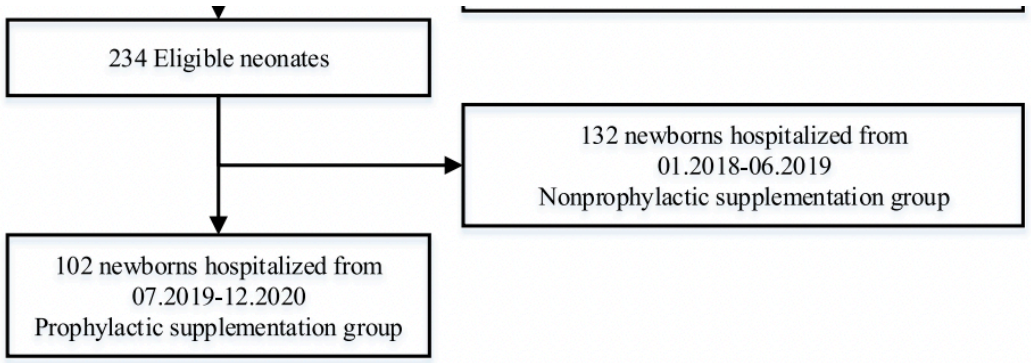
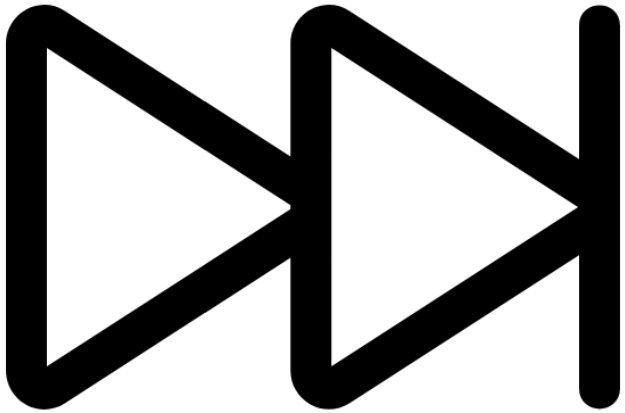


Table 1 Comparison of clinical data between the two groups

Projects	Nonprophylactic supplementation group	Prophylactic supplementation group	Statistics	*P*-value
Gestational age[M(P_{25} ~ P_{75})]/weeks	29.14(27.43 ~ 30.86)	29.57(27.86 ~ 31.14)	Z = 0.23	0.714
Birth weight[M(P_{25} ~ P_{75})]/g	1270(985.0 ~ 1552.0)	1300(1013.0 ~ 1585.0)	Z = 0.34	0.632
Gender(Male/Female, n)	71/61	55/47	χ^2 = 0.31	0.787
MBD[n(%)]	10(7.58)	2(1.96)	χ^2 = 5.53	0.023
High risk of MBD[n(%)]	48(36.36)	6(5.88)	χ^2 = 9.47	0.016
	N=132	N=102		

Metabolic Bone Disease of Prematurity

- Prevention decreases the risk of MBDP but …



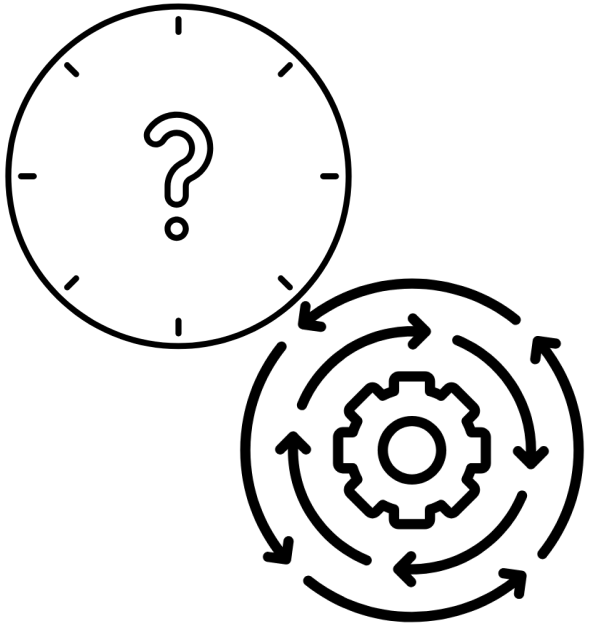
Screening for MBDP?

Table 1. Risk factors for development of MBDP

Risk factor	Mechanism
At birth	
Prematurity (<28 weeks' gestation)	Lack of in utero mineralization
Extremely (<1,000 g) and very (<1,500 g) low birth weight	Reduced placental transfer of minerals in utero
Postnatal	
PN (>4–5 weeks' duration)	Limits Ca and PO4 supplementation
Necrotizing enterocolitis	Prolonged PN Poor gut function
Chronic lung disease	High energy requirements Fluid restriction Need for glucocorticoids and loop diuretics
Reduced physical activity	Increased bone resorption Reduced bone formation
Medications	
Glucocorticoids	Increase bone resorption Reduce bone formation
Loop diuretics (furosemide)	Induce hypercalciuria
CYP450 3A4 inducers (phenobarbital)	Induce vitamin D metabolism
Methylxanthines (theophylline/caffeine)	Increase bone resorption
Anticoagulants	Reduce bone formation
Aluminum content in PN, including parenteral Ca and PO4 supplements	Reduce bone formation

Prevention

2018 ESPGHAN recommandation



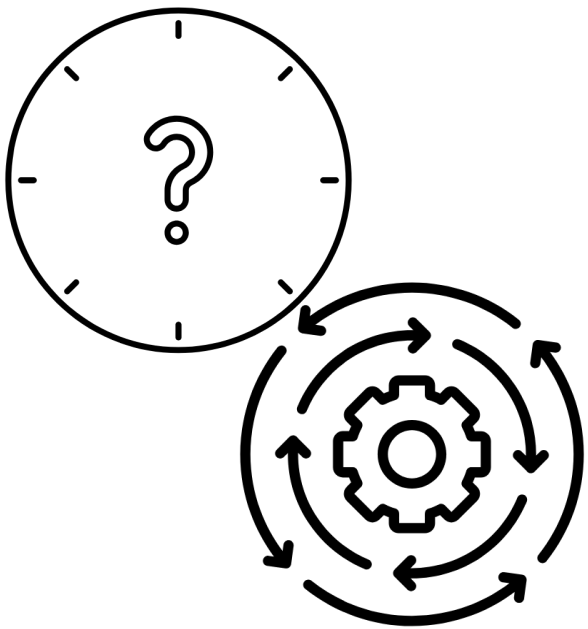
Screening for MBDP?

Table 1. Risk factors for development of MBDP

Risk factor	Mechanism
At birth	
Prematurity (<28 weeks' gestation)	Lack of in utero mineralization
Extremely (<1,000 g) and very (<1,500 g) low birth weight	Reduced placental transfer of minerals in utero
Postnatal	
PN (>4–5 weeks' duration)	Limits Ca and PO4 supplementation
Necrotizing enterocolitis	Prolonged PN Poor gut function
Chronic lung disease	High energy requirements Fluid restriction Need for glucocorticoids and loop diuretics
Reduced physical activity	Increased bone resorption Reduced bone formation
Medications	
Glucocorticoids	Increase bone resorption Reduce bone formation
Loop diuretics (furosemide)	Induce hypercalciuria
CYP450 3A4 inducers (phenobarbital)	Induce vitamin D metabolism
Methylxanthines (theophylline/caffeine)	Increase bone resorption
Anticoagulants	Reduce bone formation
Aluminum content in PN, including parenteral Ca and PO4 supplements	Reduce bone formation

Prevention

2018 ESPGHAN recommandation



When to screen?
What to screen?

When to screen?

Fracture cases

Gestational age(w)	Birth weight(g)	Days of hospitalization	Days of diagnosed	Fracture sites
27+5	1000	102	53	Femur
27+5	990	73	90	Femur
27+1	820	65	56	Femur

Xu et al, 2024

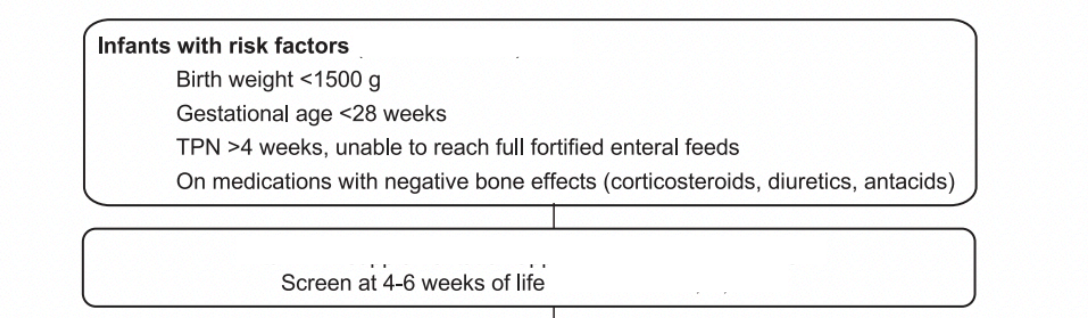
Gestational age	Birth weight	Days at diagnosis	Fracture sites
31	730	85	ribs
25+4	780	120	ribs

Yesiltepe et al 2014

Gestational age	Birth weight	Days at diagnosis	Fracture sites
29	520	49	ribs
27+6	1300	70	ribs

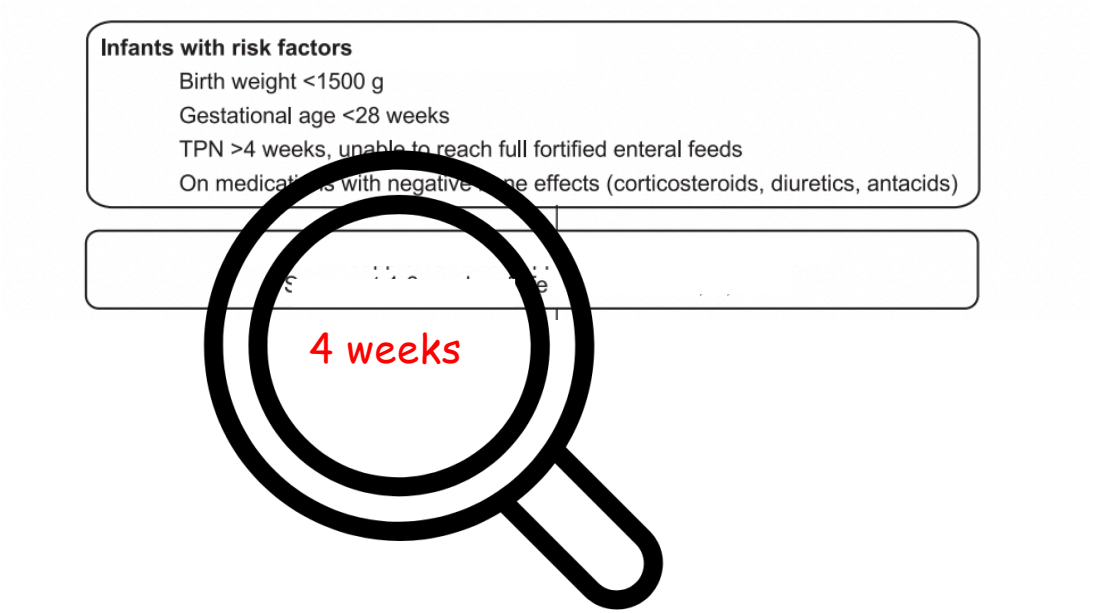
O'Reilley et al 2020

When to screen?



Chinoy et al 2019
Grover et al 2024

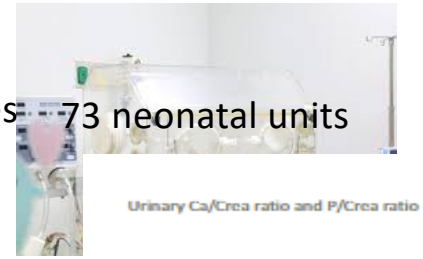
When to screen?



Grover et al 2024

What to screen?

22 countries



73 neonatal units

Received: 6 December 2023 | Revised: 30 April 2024 | Accepted: 3 May 2024

DOI: 10.1111/apa.17273

ORIGINAL ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

European survey showed wide variations in diagnostic procedures and management strategies for metabolic bone disease of prematurity in 22 countries

Luise Brado[1] | Daniel Matheisl[1] | Eva Mildenberger[2] | Hans Fuchs[1] | Daniel Klotz[1] | André Kidszun[3]

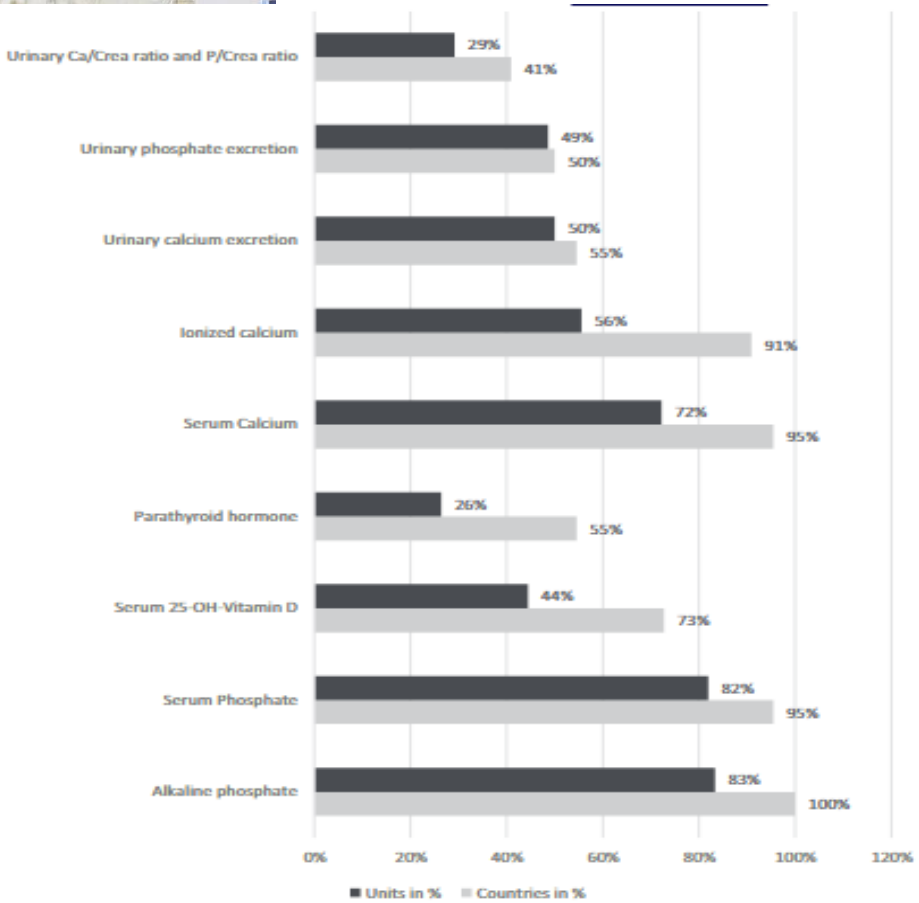
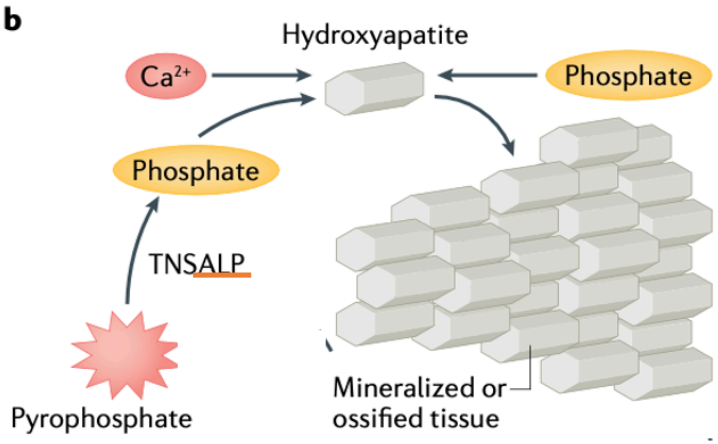
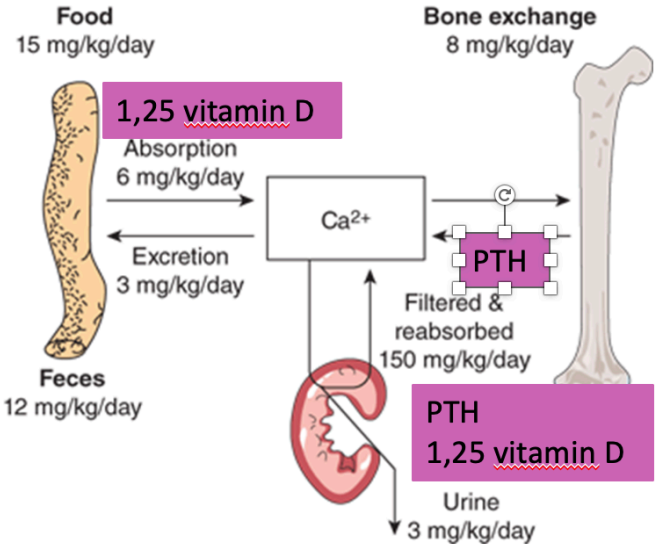


FIGURE 1 Percentage of units and countries reporting the use of biochemical blood and urine tests for the diagnosis of metabolic bone disease in preterm infants.

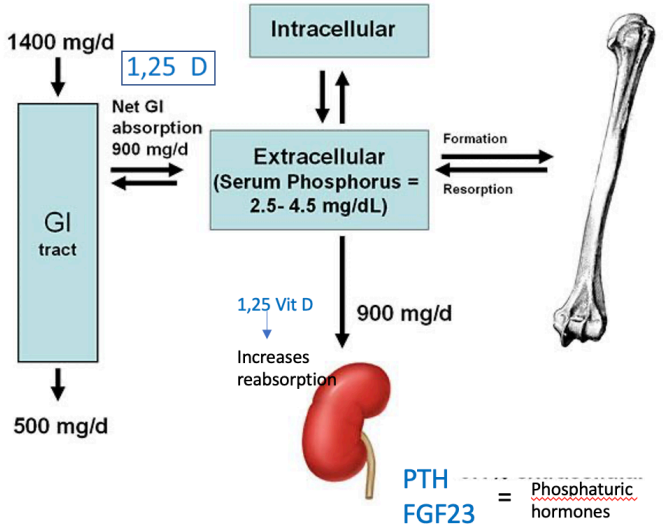
What to screen?



Calcium



Phosphate



Mineral homeostasis

Low calcium intake

↓

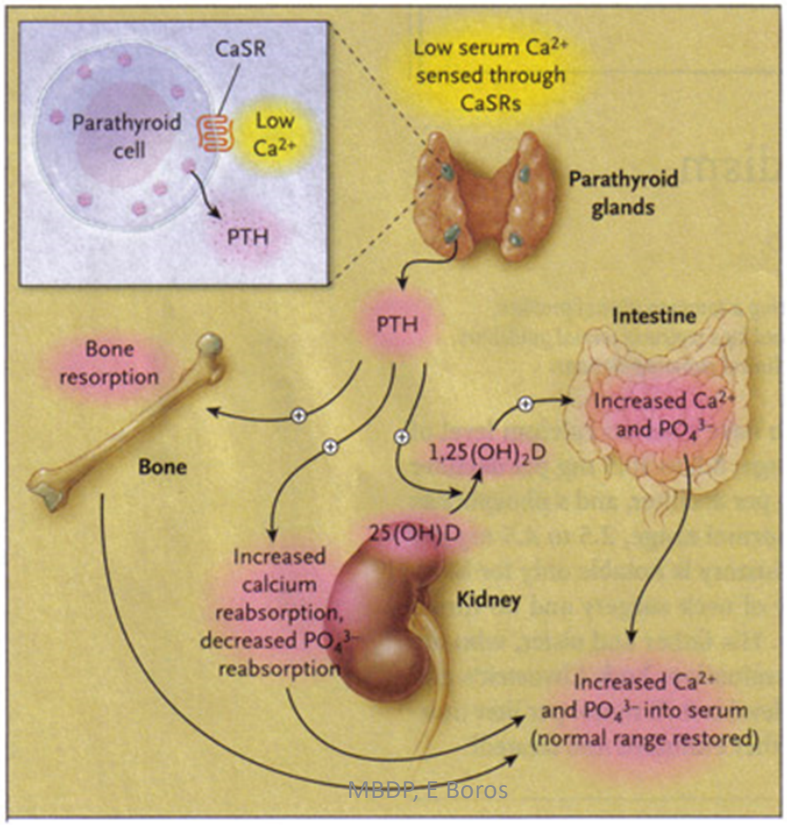
□ PTH

↓

□ urinary phosphate=> low TRP

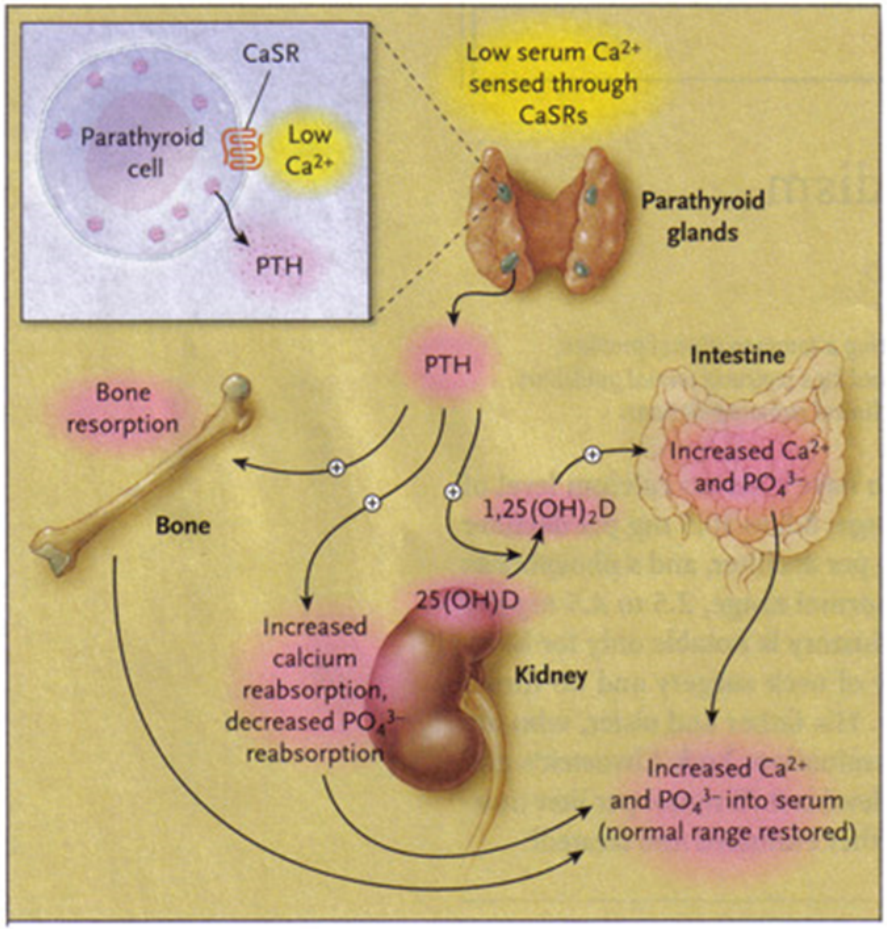
↓

Normal serum calcium
Low serum phosphate



Shoback et al, NEJM 2008

Mineral homeostasis



Low phosphate intake

↓

normal PTH

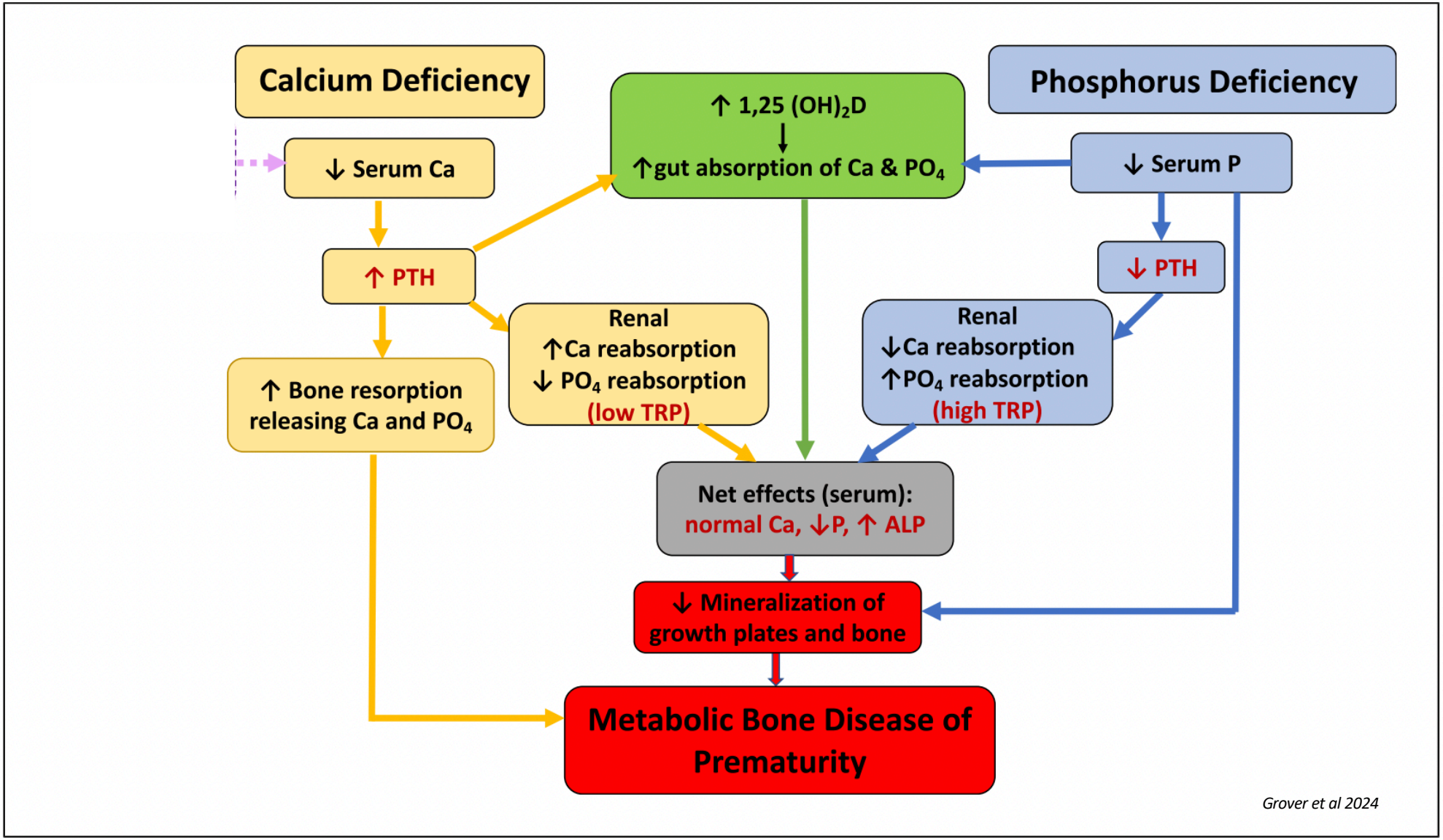
↓

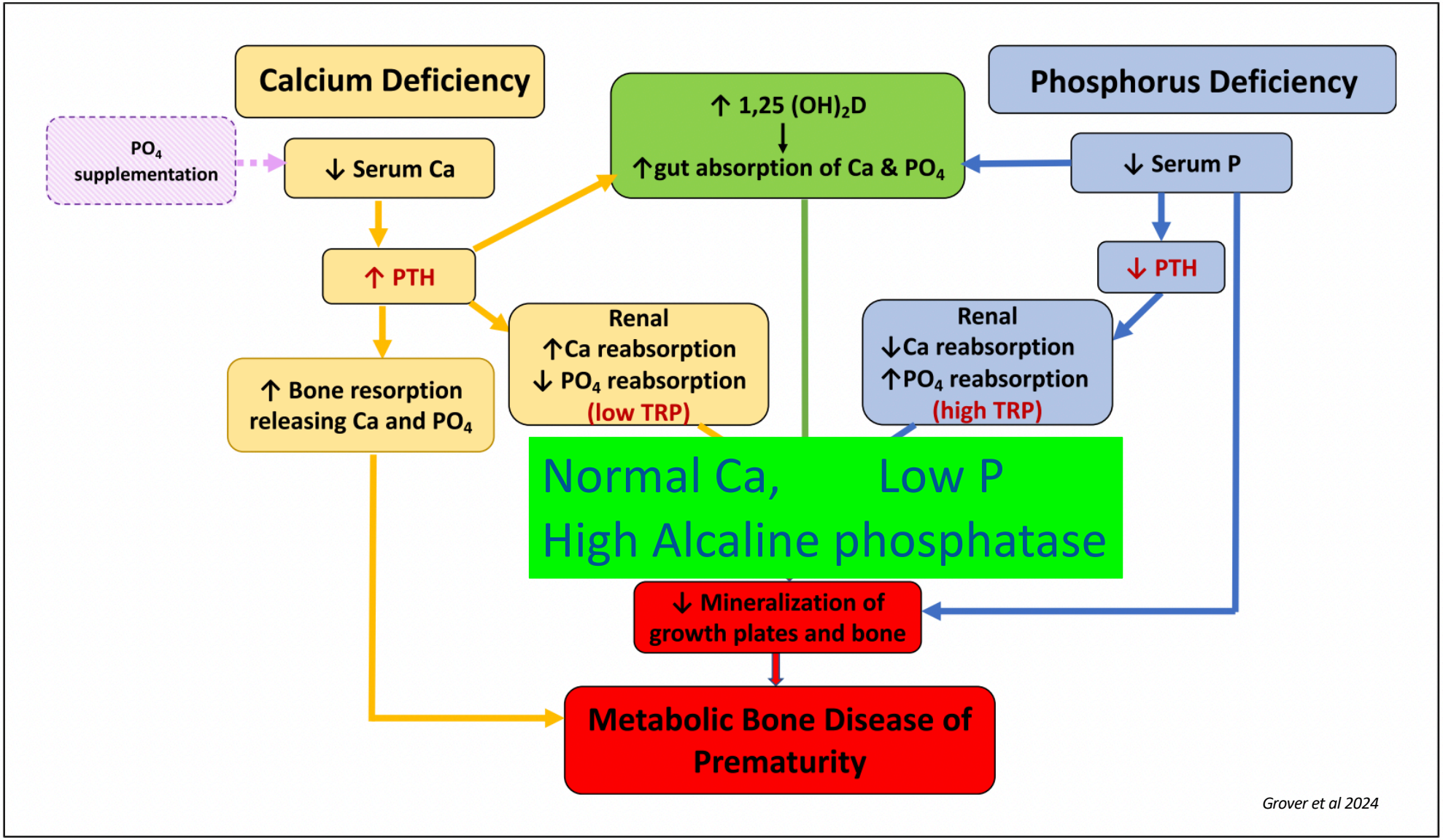
Normal/low urinary phosphate=> high TRP

↓

Normal serum calcium
Low serum phosphate

Shoback et al, NEJM 2008


Calcium Deficiency
↓ Serum Ca
↑ PTH
↑ Bone resorption releasing Ca and PO_4
↑ 1,25 $(OH)_2D$
↑gut absorption of Ca & PO_4
Renal
↑Ca reabsorption
↓ PO_4 reabsorption
(low TRP)
Phosphorus Deficiency
↓ Serum P
↓ PTH
Renal
↓Ca reabsorption
↑PO_4 reabsorption
(high TRP)
Net effects (serum):
normal Ca, ↓P, ↑ ALP
↓ Mineralization of growth plates and bone
Metabolic Bone Disease of Prematurity
Grover et al 2024


Calcium Deficiency
Phosphorus Deficiency
PO_4 supplementation
↓ Serum Ca
↑ 1,25 $(OH)_2D$
↑gut absorption of Ca & PO_4
↓ Serum P
↑ PTH
↓ PTH
Renal
↑Ca reabsorption
↓ PO_4 reabsorption
(low TRP)
Renal
↓Ca reabsorption
↑PO_4 reabsorption
(high TRP)
↑ Bone resorption releasing Ca and PO_4
Normal Ca, Low P
High Alcaline phosphatase
↓ Mineralization of growth plates and bone
Metabolic Bone Disease of Prematurity
Grover et al 2024

What to screen?

- Alcaline phosphatase
- Phosphate
- Calcium

When and what to screen?

Grover et al 2024

Normal values

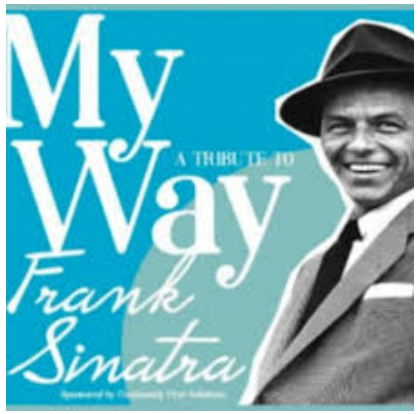
Received: 6 December 2023 | Revised: 30 April 2024 | Accepted: 3 May 2024
DOI: 10.1111/apa.17273

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

European survey showed wide variations in diagnostic procedures and management strategies for metabolic bone disease of prematurity in 22 countries

Luise Brado[1] | Daniel Matheisl[1] | Eva Mildenberger[2] | Hans Fuchs[1] | Daniel Klotz[1] | André Kidszun[3]



MBDP, E Boros

TABLE 3 Cut-off values reported by participating units.

Marker	Reported ranges of cut-off values	Most often reported cut-off value
Ionised calcium	<0.8–1.3 mmol/L	
Serum calcium	<1.5–2.7 mmol/L	<2.2 mmol/L
Serum phosphate	<1.1–2.2 mmol/L	<1.8 mmol/L
Alkaline phosphatase	>400–1200 U/L	>800 U/L >500 U/L
Parathyroid hormone	>40–100 pg/mL	
Urinary calcium	Lower cut-off value <0.5 mmol/L Upper cut-off value >2 mmol/L	<1 to >3 mmol/L
Urinary phosphate	Lower cut-off value <1 mmol/L Upper cut-off value >5 mmol/L	<1 to >5 mmol/L
Urinary calcium creatinine ratio	Lower cut-off value <0.09 Upper cut-off value >0.4	
Urinary phosphate creatine ratio	Lower cut-off value <0.8 Upper cut-off value >2.5	
Tubular phosphorus reabsorption	No cut-off value	
Urine fractional phosphate excretion	>95%	

Normal values

Diagnostic markers of metabolic bone disease of prematurity in preterm infants

Kui-Lin Lü [a 1], Shuang-Shuang Xie [b 1], Qi Hu [c 1], Zhang-Ya Yang [a], Qiong-li Fan [a], En Liu [d], Yu-Ping Zhang [a]

2023

- Alkaline phosphatase 344 U/L is a cutoff for an early warning of metabolic bone disease in premature infants.

Practical approach to managing metabolic bone disease of prematurity in the neonatal unit

Chris Forster [1], Shazia Hoodbhoy,[2] Catriona Macdougall,[2] Karen King,[3] Nigel Gooding,[4] Kimberly Mak,[5] Talat Mushtaq [6]

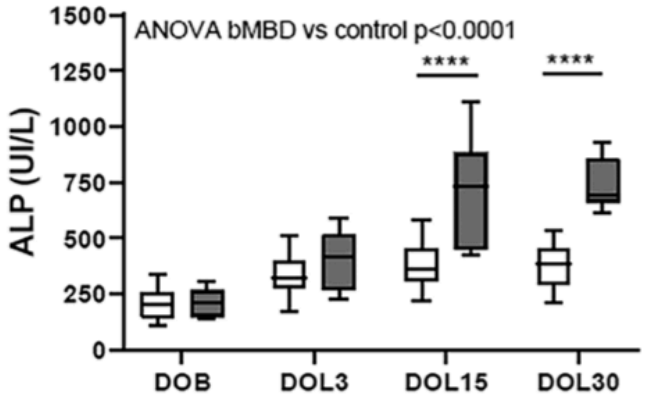
2023

MBDP= ALP >700 IU/L

MBDP, E Boros

Normal values

Alcaline phosphatase



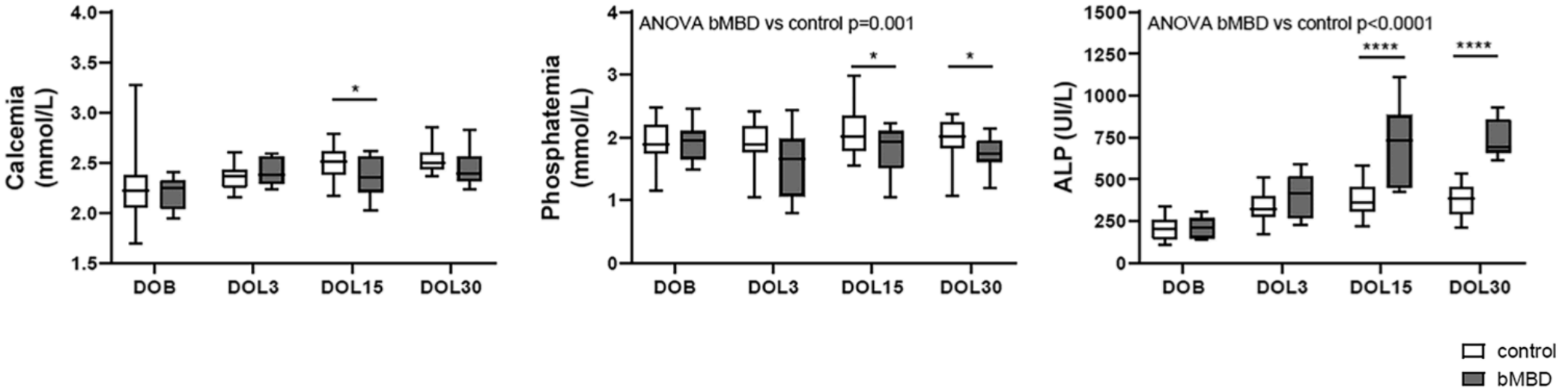
Threshold ALP of 500 U/l at 1 month

control
bMBD

DOB= day of birth
DOL= day of life

Motte-Signoret et al 2023

Normal values



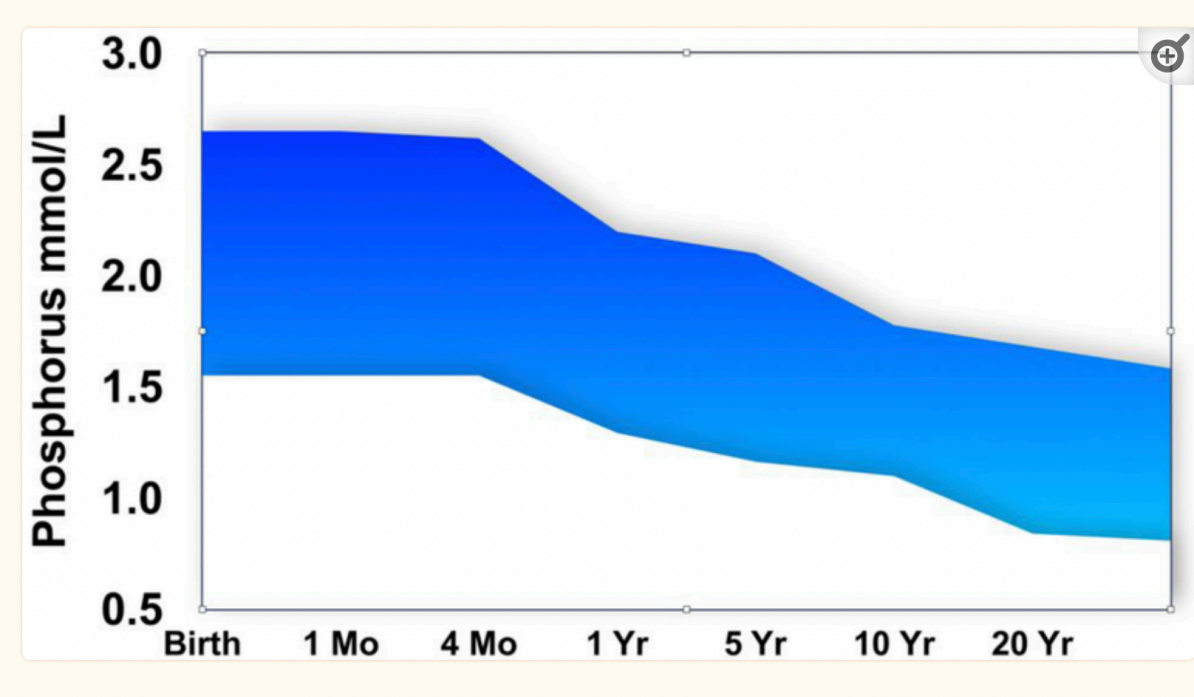
Conclusions: Our results showed that even the strict respect of nutritional guidelines cannot completely prevent bMBD in high-risk patients and suggest that an early screening from DOL15, with ALP levels greater than 500 UI/L, could be sufficient for detection of upcoming MBD.

DOB= day of birth
DOL= day of life

Motte-Signoret et al 2023

Normal values

Phosphate



Age groups	Phosphate level (mmol/L)
<3 months	1.55-2.4
3-12 months	1.55-2.2
1-4 years	1.29-2.2
5-11 years	1.19-2.1
12-18 years	1.1-1.9

Imel et al 2020

Thresholds

Threshold	Keypoints
ALP >500 IU/L trending up >800 IU/L more commonly associated with rickets	- Physiologic elevation for the first 4-6 weeks - Can be elevated in liver disease - May be low in glucocorticoid treatment
Phosphate <1.8 mmol/l (5.5 mg/dl) < 1.5 mmol/l (4.5 mg/dl) more sensitive	- Persistently low phoshate increases the risk of MBDP
Calcium <2.1 mmol/l (8.5 mg/dl) > 2.6 mmol/l (10.5 mg/dl)	- Isolated measurements not useful

Adapted from Grover 2024 and Figueras-Aloy 2014

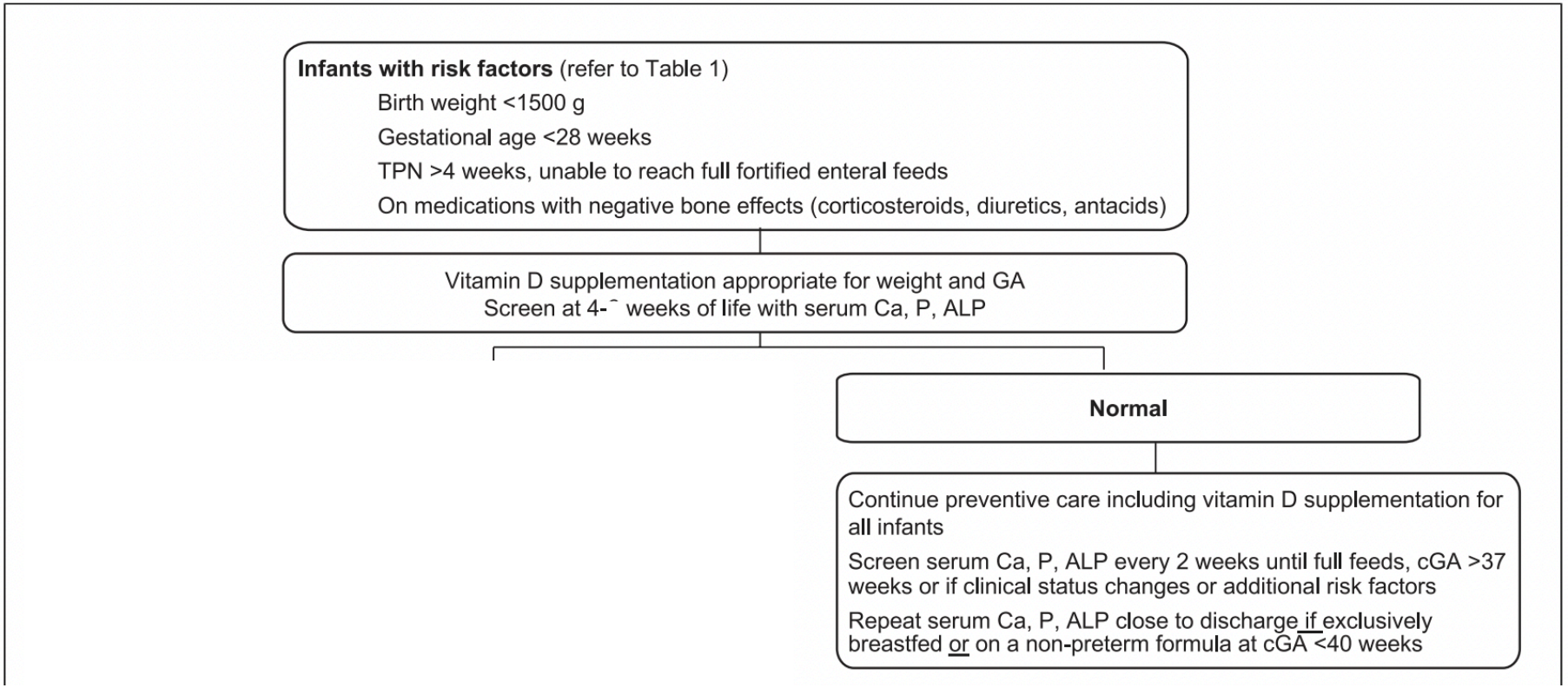
Diagnostic of MBDP
at 4 weeks

Threshold	Keypoints
ALP >500 IU/L trending up >800 IU/L more commonly associated with rickets	- Physiologic elevation for the first 4-6 weeks - Can be elevated in liver disease - May be low in glucocorticoid treatment
Phosphate <1.8 mmol/l (5.5 mg/dl) < 1.5 mmol/l (4.5 mg/dl) more sensitive	- Persistently low phoshate increases the risk of MBDP
Calcium <2.1 mmol/l (8.5 mg/dl) > 2.6 mmol/l (10.5 mg/dl)	- Isolated measurements not useful

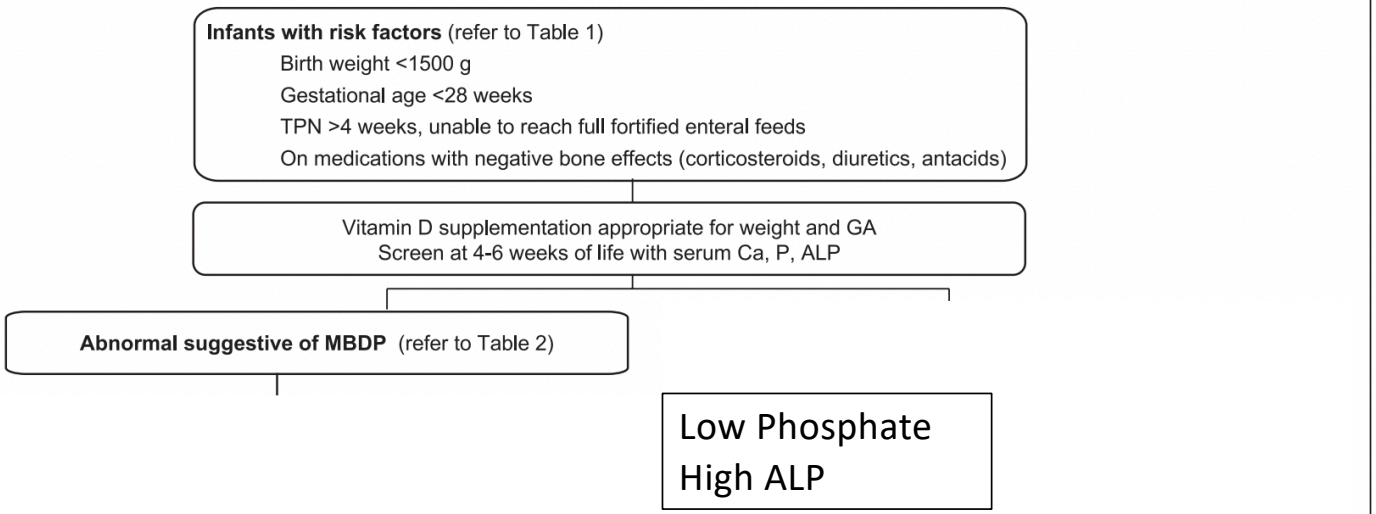
1. ALP>800 IU/L or P<1.5 mmol/l
2. ALP>500IU/l and P<1.8 mmol/l

Adapted from Grover 2024 and Figueras-Aloy 2014

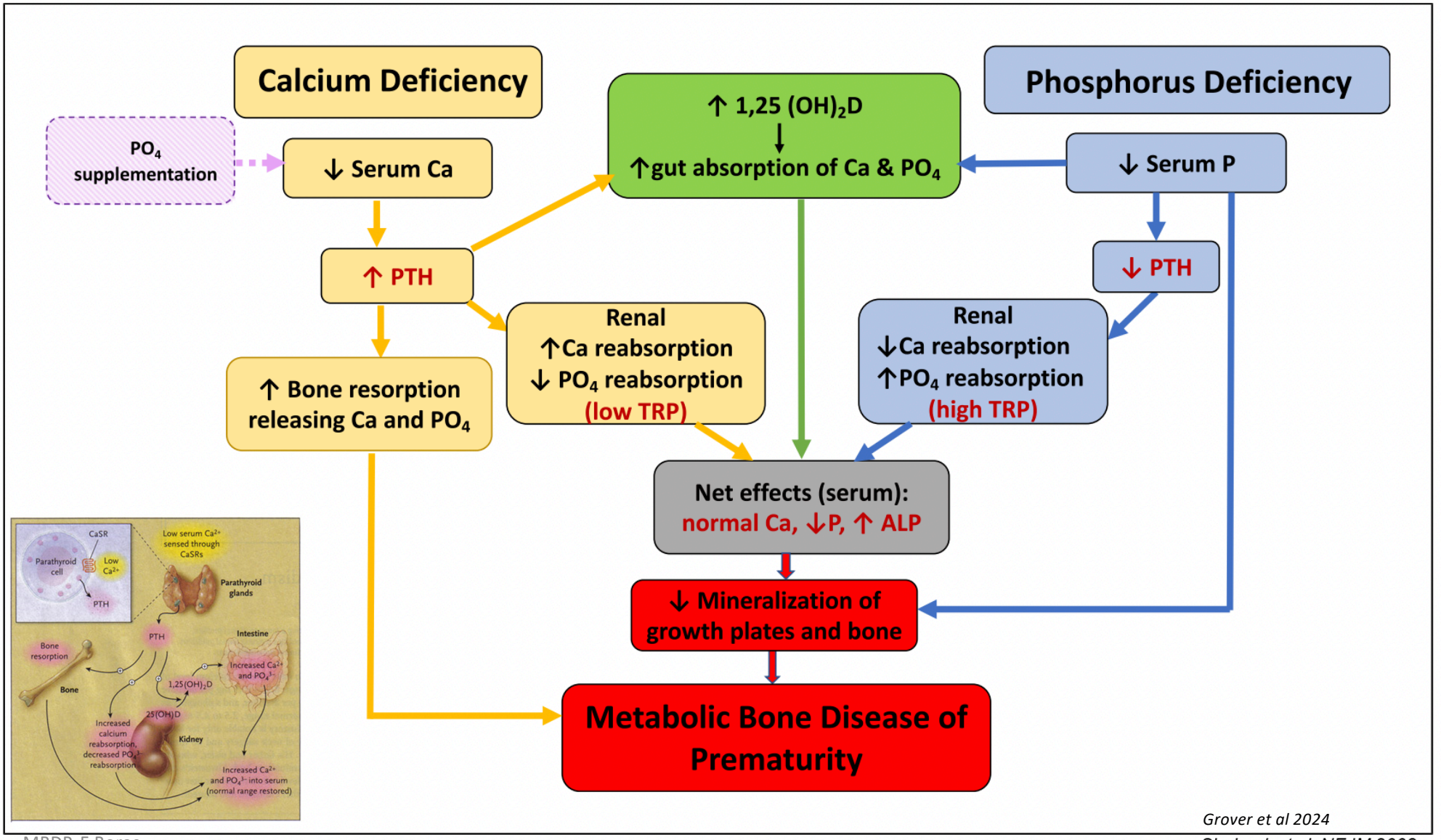
No MBDP



Grover et al 2024



Grover et al 2024



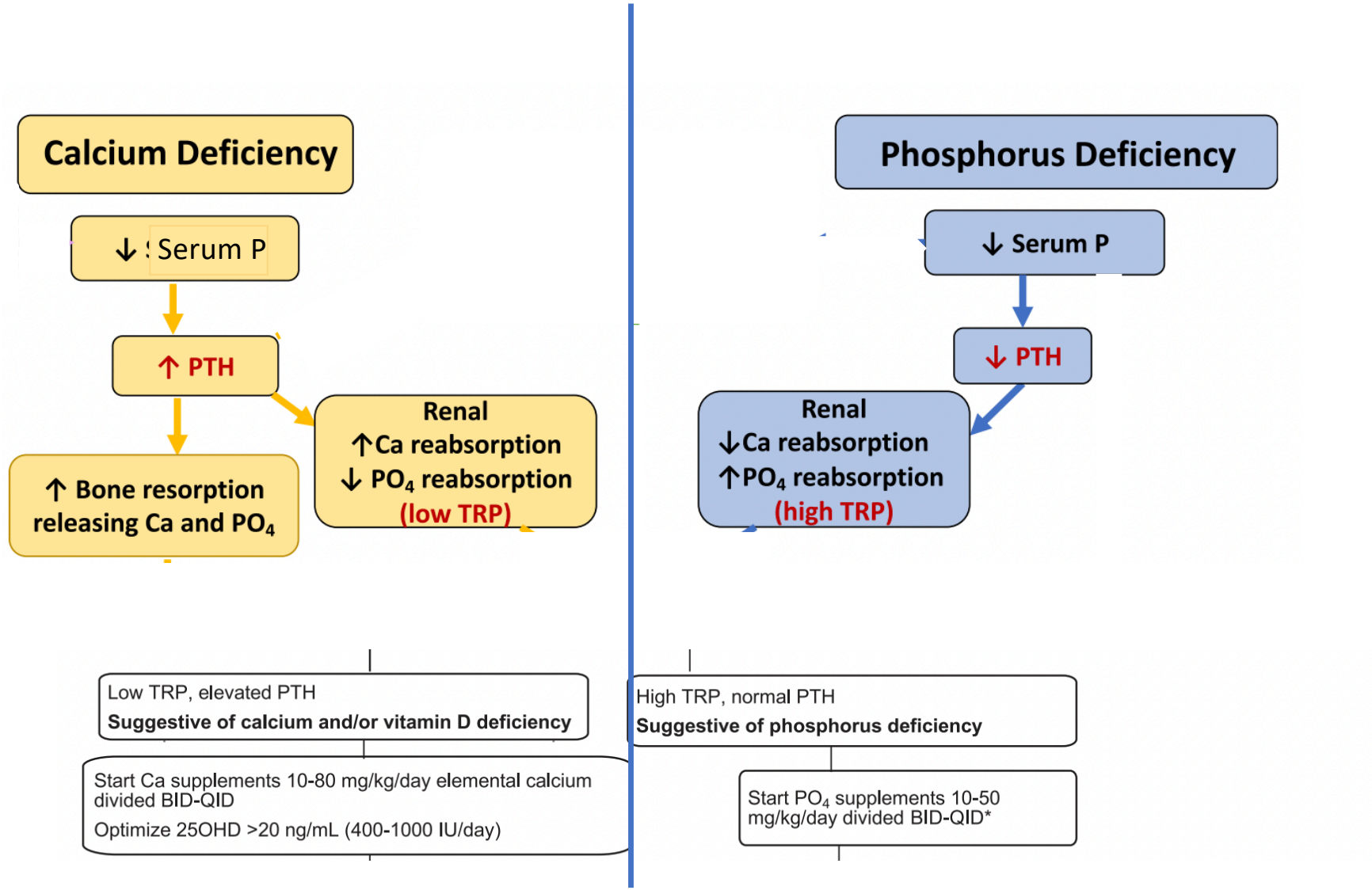
Grover et al 2024

Shoback et al, NEJM 2008

Normal values

Threshold	Keypoints
PTH >100 pg/ml	Reference range similar to adults
TRP >95% in the setting of low phosphate normal range 78-91% in preterms	High TRP suggests near complete urinary reabsorption and suggests phosphate supplementation Low TRP suggests excess urinary phosphate excretion, associated with high PTH

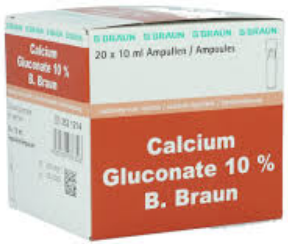
Adapted from Grover et al 2024



Adapted from Grover et al 2024

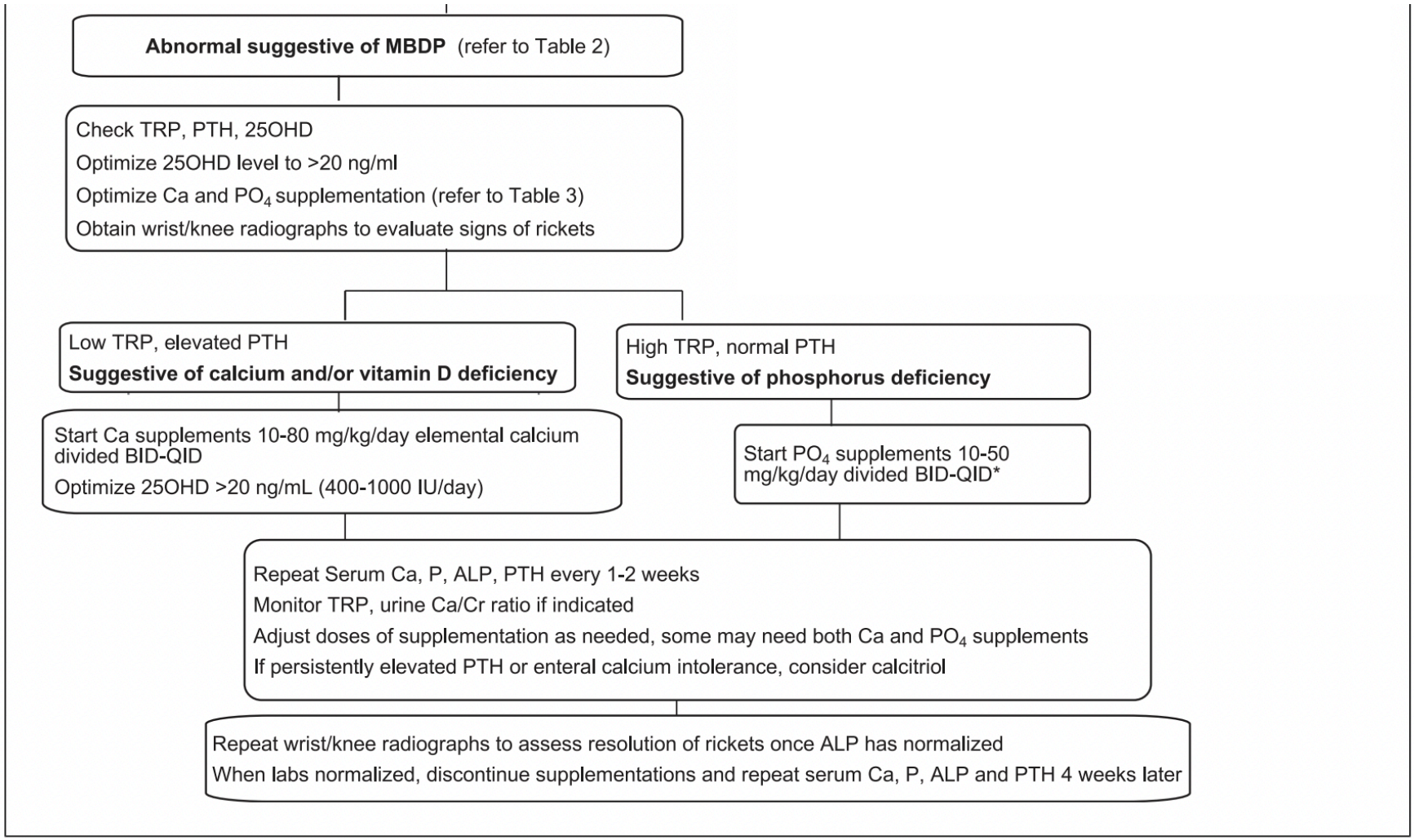
Supplementation

Product	Content in mineral
Calcium	
Calcium gluconate (solution)	94 mg of elemental calcium/1 ml
Calcium carbonate	40 mg of elemental calcium/100 mg
Phosphate	
Potion Joulie	30 mg of elemental phosphate/1 ml



Potion Joulie

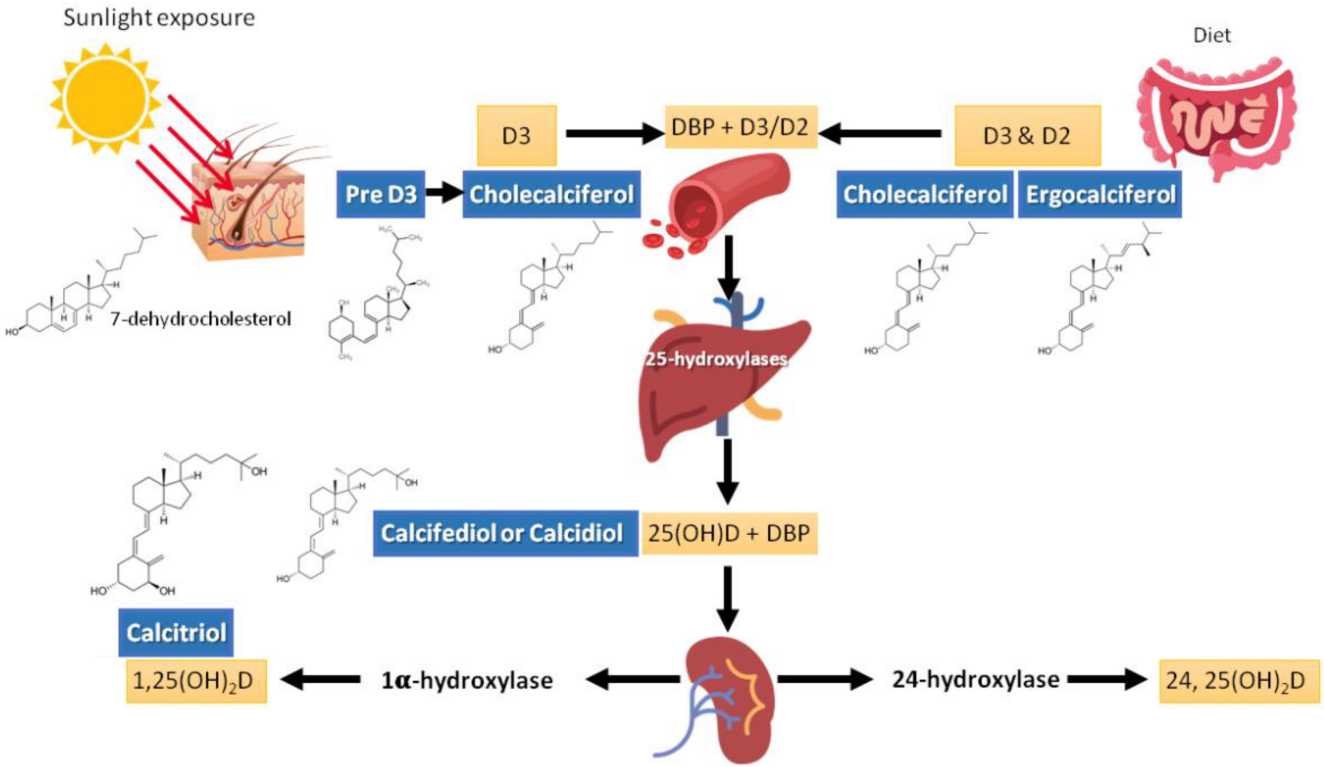
Na2HPO4 . 12H2O		13,6g
H3PO4		5,88g
H2O	AD	100ml



MBDP, E Boros

Grover et al 2024

Vitamin D


Sunlight exposure
Diet
D3
DBP + D3/D2
D3 & D2
Pre D3
Cholecalciferol
Cholecalciferol
Ergocalciferol
7-dehydrocholesterol
25-hydroxylases
Calcifediol or Calcidiol
25(OH)D + DBP
Calcitriol
1,25(OH)2D
1α-hydroxylase
24-hydroxylase
24, 25(OH)2D

Vitamin D in preterms

Optimal level
25 OH vitamin D >20 ng/ml

More respiratory distress

200-400 UI *vs* 960 UI

Backström et al.
Finland

Less complications

400UI vs 800 UI

El-Beltagi et al
Egypt

No deficiency at 28 days

200UI/ 400UI/ 1000 UI

Fort et al USA

Lower ALP

400 UI *vs* 1000 UI

Mahur et al.
India

Vitamin D in preterms

Optimal level
25 OH vitamin D >20 ng/ml

- 800 IU if born <32 w
- 400 IU if born >32 w
- If risk group follow serum level

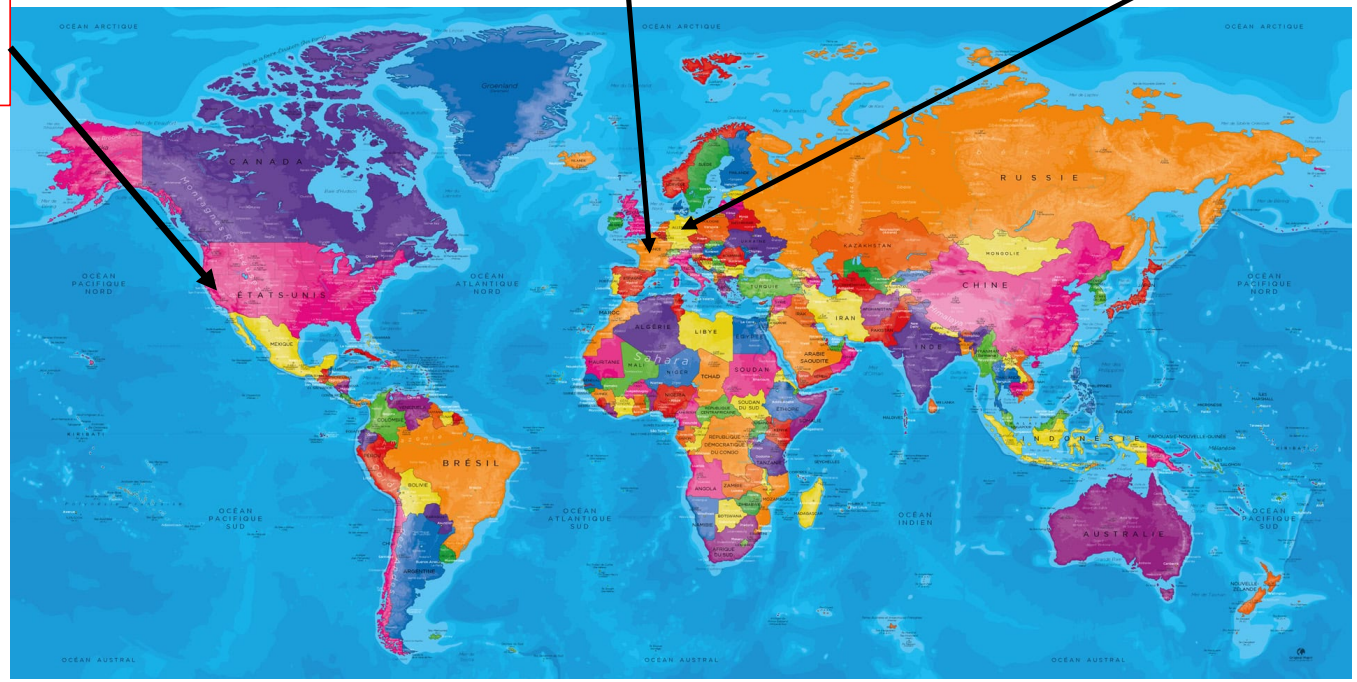
Pludowski et al 2023

-During the initial stay in the NICU, 600 IU – 1000 IU

Bachetta et al 2022

-400 IU if BW<1500g
-200-400 IU if BW>1500g

Abrams et al 2013
Grover et al 2024



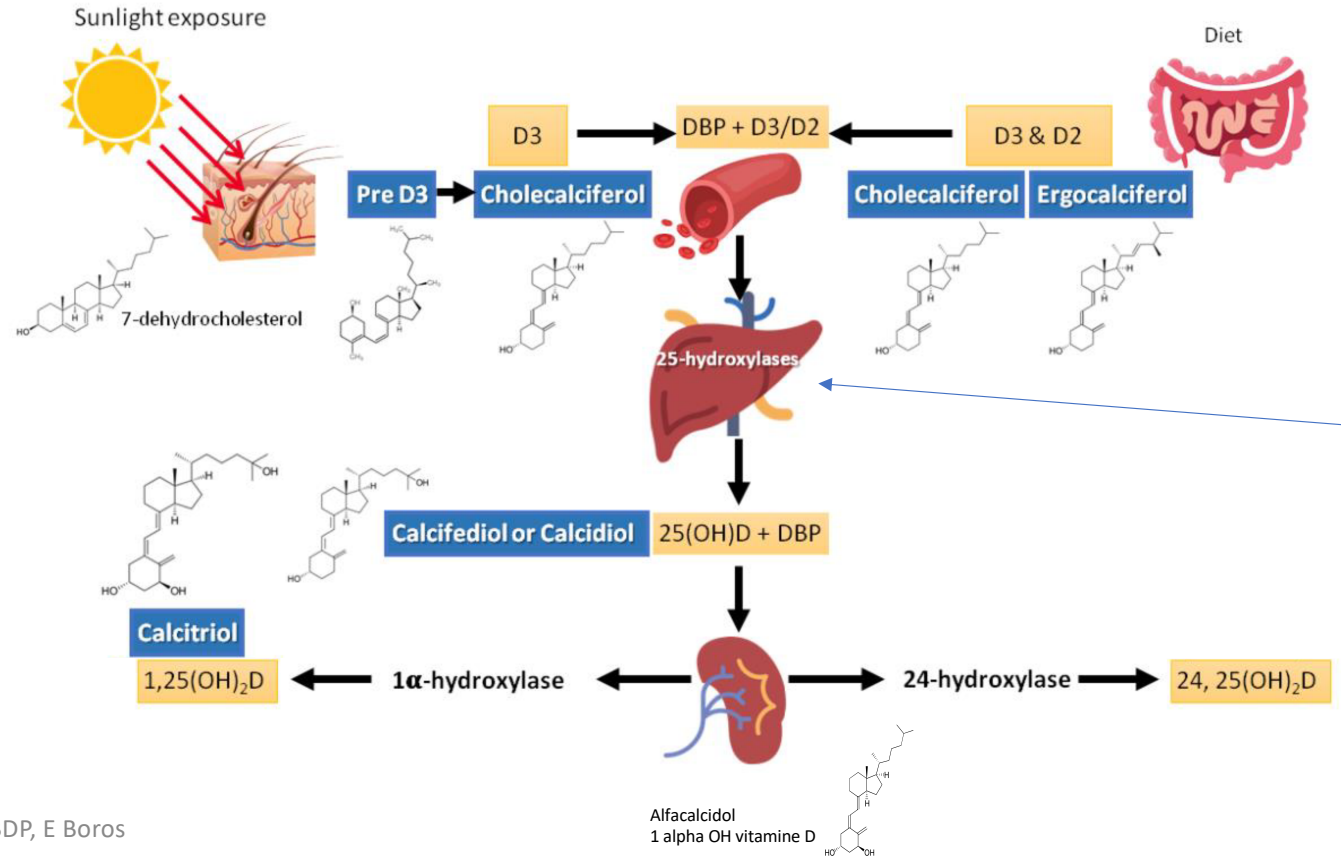
Vitamin D status in a Belgian cohort

			Age
			<1
Vitamin D status	Severely deficient <12 ng/mL	Count (*n*)	526
		Percentage	22.3%
	Insufficient 12–20 ng/mL	Count (*n*)	547
		Percentage	23.2%
	Borderline 20–30 ng/mL	Count (*n*)	521
		Percentage	22.1%
	Sufficient >30 ng/mL	Count (*n*)	760
		Percentage	32.3%
	Total	Count (*n*)	2354

Van de Waele et al 2024

Vitamin D in preterms

- Starting dose: 400 UI-1000 UI/day
- Adapt at 4 weeks depending on 25 OHD result

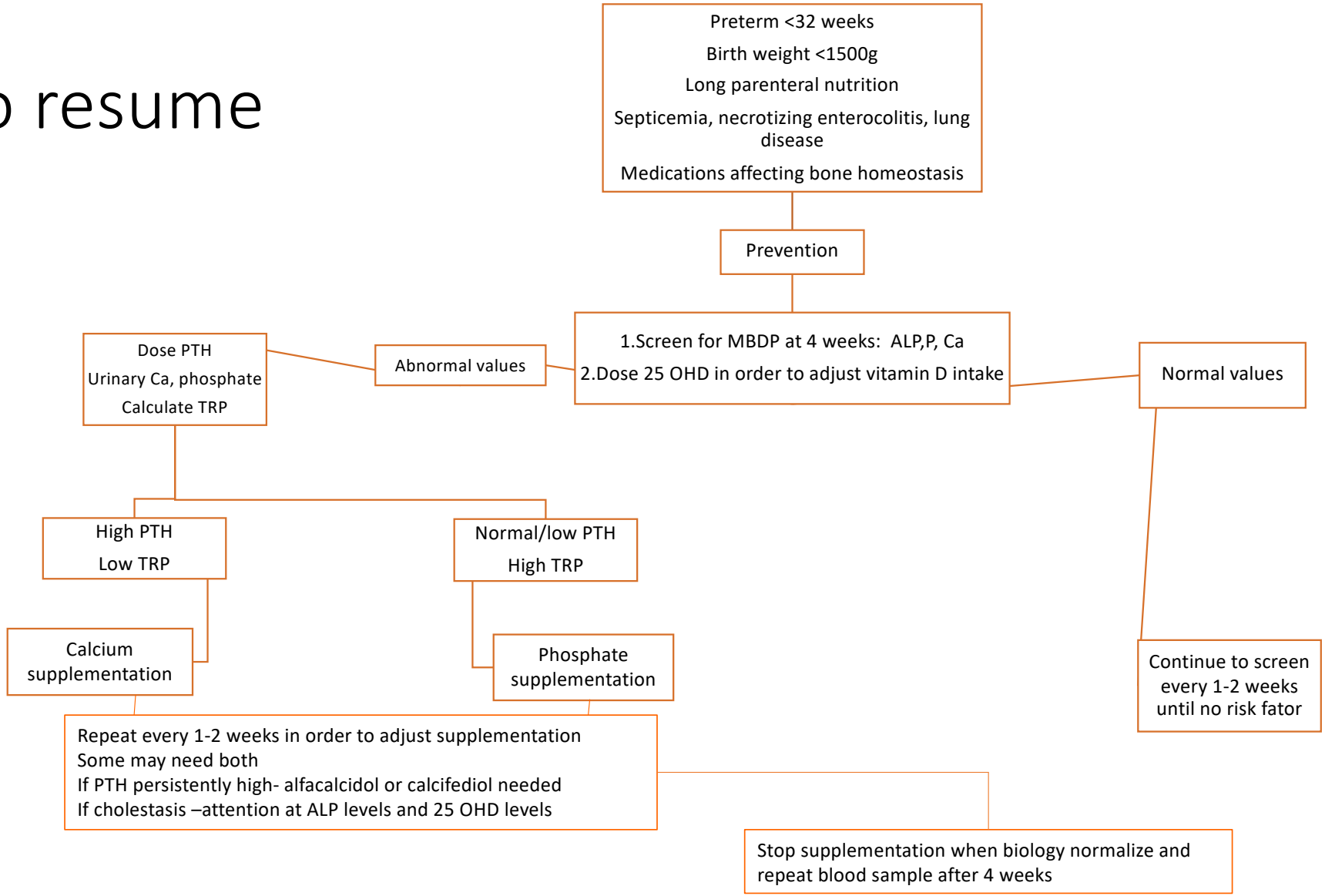


- If levels of 25 OH vit D stays low despite higher intake of vitamin D
- High PTH levels despite normal intake

Give calcifediol or alfacalcidol

MBDP, E Boros

To resume


Preterm <32 weeks
Birth weight <1500g
Long parenteral nutrition
Septicemia, necrotizing enterocolitis, lung disease
Medications affecting bone homeostasis
Prevention
1.Screen for MBDP at 4 weeks: ALP,P, Ca
2.Dose 25 OHD in order to adjust vitamin D intake
Abnormal values
Dose PTH
Urinary Ca, phosphate
Calculate TRP
Normal values
High PTH
Low TRP
Normal/low PTH
High TRP
Calcium supplementation
Phosphate supplementation
Continue to screen every 1-2 weeks until no risk fator
Repeat every 1-2 weeks in order to adjust supplementation
Some may need both
If PTH persistently high- alfacalcidol or calcifediol needed
If cholestasis –attention at ALP levels and 25 OHD levels
Stop supplementation when biology normalize and repeat blood sample after 4 weeks

Take home message

- MBDP can have short and longterm consequences
- Prevention is the initial goal
    - Respect Espghan recommendation of supplementation via parenteral nutrition
    - As soon as possible enteral nutrition with fortified breast milk or preterm formula
- Screen at 4 weeks: ALP, P + dose 25 OHD
    - Very preterm infants
    - Low birth weight infants
    - Sick infants

Take home message

- If MBDP treat with
  - Calcium if high PTH and low TRP
  - Phosphate if normal PTH and high TRP
- Repeat investigations every 1-2 weeks
- Normal lab= stop treatment and repeat after 4 weeks

- Vitamin D deficiency is not the cause but can worsen MBDP


THANK YOU
FOR YOUR ATTENTION