# METABOLIC BONE DISEASE
## Supporting information

**This guideline has been produced with reference to the following:**

Faienza MF, D'Amato E, Natale MP et al. Metabolic Bone Disease of Prematurity: Diagnosis and Management. Front Pediatr. 2019;7:143

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6474071/

Erol I, Buyan N, Ozkaya O et al. Reference values for urinary calcium, sodium and potassium in healthy newborns, infants and children. Turk J Pediatr. 2009;51:6-13

**Which biochemical marker should be used to identify metabolic disease in preterm infants?**
None of the evaluated metabolites (Ca, $PO_4$, ALP and vitamin D) alone can be considered a marker of metabolic bone disease (MBD) of prematurity. In a study (Figueras-Aloy 2014) in 336 preterm infants who underwent biochemical analyses and bone mineral density (BMD) assessment; the closest correlations between BMD and any other variables were seen for ALP and $PO_4$. The concentration threshold of ALP to indicate MBD was 500 IU/L, and the maximum value of the correlation (0.290) was obtained by associating the ALP and $PO_4$ concentrations with a cut off point of 4.5 mg/dL (1.45mmol/L) to differentiate mild from severe MBD. According to Hung et al, an ALP level >700 IU/L at 3 weeks postnatal age was predictive of osteopenia at term, with a sensitivity of 73% and a specificity of 74%. In another study (Backstrom 2000) in 43 preterm infants, a combination of the criteria "serum total ALP> 900 IU/l" and "serum $PO_4$ <1.8 mmol/l" yielded a sensitivity of 100% at a specificity of 70% in revealing low BMD by dual energy X-ray absorptiometry. In a cohort study of 64 VLBW infants, higher values of urinary Ca (MBD = 31.9 +/- 20.2, without MBD = 19.8 +/- 15.4; p = 0.017) and ALP (MBD = 369 +/- 114, without MBD = 310 +/- 93; p = 0.04) were found in infants who developed MBD. In a systematic review by Visser et al, it was suggested that none of the frequently used serum measurements are valid biochemical markers of MBD in preterm infants.

Backstrom MC, Kouri T, Kuusela AL et al. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. Acta Paediatrica. 2000; 89: 867-73

Catache M, Leone CR. Role of plasma and urinary calcium and phosphorus measurements in early detection of phosphorus deficiency in very low birthweight infants. Acta Paediatr. 2003;92:76-80

Figueras-Aloy J, Álvarez-Domínguez E, Pérez-Fernández JM et al. Metabolic bone disease and bone mineral density in very preterm infants. J Pediatr. 2014 Mar;164:499-504
http://www.sciencedirect.com/science/article/pii/S0022347613013851

Hung YL1, Chen PC, Jeng SF et al. Serial measurements of serum alkaline phosphatase for early prediction of osteopaenia in preterm infants. J Paediatr Child Health. 2011;47(3):134-9.

Visser F1, Sprij AJ, Brus F. The validity of biochemical markers in metabolic bone disease in preterm infants: a systematic review. Acta Paediatr. 2012 Jun;101:562-8

**Evidence Level: III**

**What is the role of monitoring urinary mineral excretion to guide mineral supplementation?**
An interventional cohort study (Pohlandt 1994) demonstrated that infants who simultaneously excreted Ca >1.2 mmol/L and PO4 at >0.4 mmol/L (in spot urinary specimens) by means of an individual supplementation with Ca and/or PO4 resulting in a slight surplus supply showed the highest bone mineral accretion measured by single-photon absorption densitometry. Hence, an individualized Ca and $PO_4$ supplementation in preterm infants aiming for a slight excess of the actual need, guided by urinary Ca and $PO_4$ concentrations, appears to be able to achieve fetal mineralisation rate. The above strategy appears sensible as both growth velocity and enteral Ca absorption are highly variable. However, monitoring of urinary Ca and $PO_4$ concentrations needs to take into account non-nutritional factors affecting these concentrations in particular drug related calciuria and phosphaturia. Specifically, methylxanthines and diuretics increase the renal Ca losses, and the renal $PO_4$ threshold may be lowered in premature infants. Infants between 26 and 31 weeks were found to have a renal $PO_4$ threshold in the range of normal serum $PO_4$ values (2 mmol/L) but Hellstern et al have shown that extremely preterm infants (23-25 weeks) had a much lower renal $PO_4$ threshold, leading to

urinary $PO_4$ excretion even in the presence of low $PO_4$ levels. In a recent study (Mihatsch 2012) in infants born preterm on regular 3 or 4 h feedings, 6 h urine sampling was shown to be sufficiently precise for prediction of Ca and $PO_4$ deficiency homeostasis (PPV 0.92 and 0.83) defined as 24 h urinary concentrations <1 mmol/l Ca or $PO_4$. As urinary ratios depend heavily on type of feed as mentioned in the guideline, standard reference ranges are less useful.

Hellstern G, Poschl J, Linderkamp O. Renal phosphate handling of premature infants of 23–25 weeks gestational age. Ped Nephr 2003; 18: 756–8.

Mihatsch W, Trotter A, Pohlandt F. Calcium and phosphor intake in preterm infants: sensitivity and specifity of 6-hour urine samples to detect deficiency. Klin Padiatr. 2012 Mar;224:61-5

Pohlandt F. Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. Pediatr Res 1994;35:125–129

Trotter A, Pohlandt F. Calcium and phosphorus retention in extremely preterm infants supplemented individually. Acta Paediatr 2002;91:1–4

**Evidence Level: III**

**Which method of monitoring urine mineral excretion should be used- urinary Ca or $PO_4$ concentrations or Ca/creatinine(Cr) or $PO_4$ /creatinine ratios?**

It is unclear whether the Ca/Cr and $PO_4$/Cr ratios are superior to the simple urinary Ca and $PO_4$ concentrations. Aladangady et al reported a reference range for urinary Ca/Cr and $UPO_4$/Cr ratios and factors influencing these ratios in a representative population of preterm infants between 24- 34 weeks gestation but to date no study has shown that these variables are a reliable surrogate measure of bone mineral content. It is well known that urinary Ca and PO4 concentrations vary and that Cr corrects for varying urine volumes that depend on fluid intake. However, in the slight surplus supply concept, the exact daily amount of Ca/ $PO_4$ excretion is not the primary target as simple urinary Ca and $PO_4$ concentrations indicate whether there is a surplus (>1 mmol/l) or not (<1 mmol/l). In addition, most stable growing preterm infants are on a constant daily fluid intake and fed at regular intervals during the day and night. Consequently there are no circadian variations in urinary mineral concentrations. Boehm et al described a correlation between the real daily excretion and the mean substrate/ Cr ratio of a 24-h collection period, which was weaker than the correlation between the 6-h and the 24-h excretion of the respective substrates. A correction for the urine volume therefore does not seem to be of importance and would actually increase the costs (Cr measurement). In a recent study (Staub 2014), comparison of urinary mineral concentration with mineral/Cr ratio with the intention to supplement the respective mineral, was shown to be moderate for Ca and good for $PO_4$ but the results did not allow for identifying superiority of either method on the decision to supplement. $PO_4$ is not bound in the plasma like Ca and so the percent tubular reabsorption of $PO_4$ (TRP) is the best guide to adequacy of $PO_4$ supplementation. A percent TRP of >95% shows inadequate supplementation. However, this must be taken in relation to plasma Ca; inadequate Ca intake will lead to hyperparathyroidism and hence tubular leak of $PO_4$. Similarly, if $PO_4$ intake is low, there is breakdown of bone and hence release of Ca leading to hypercalcaemia and calciuria. TRP can be calculated using the formula:

%TRP = 1 − Urine $PO_4$/Urine creatinine× Plasma creatinine/Plasma phosphate× 100.

Aladangady N, Coen PG, White MP et al. Urinary excretion of calcium and phosphate in preterm infants. Pediatric Nephrology. 2004; 19: 1225-31

Boehm G, Wiener M, Schmidt C et al. Usefulness of short-term urine collection in the nutritional monitoring of low birthweight infants. Acta Paediatr 1998;87:339–343

Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretations. Ann Clin Biochem 1998; 35: 201–6

Pohlandt F. Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. Pediatr Res 1994;35:125–129

Pohlandt F, Mihatsch WA. Reference values for urinary calcium and phosphorus to prevent osteopenia of prematurity. Pediatr Nephrol 2004;19:1192–1193

Staub E, Wiedmer N, Staub LP et al. Monitoring of urinary calcium and phosphorus excretion in preterm infants: comparison of 2 methods. J Pediatr Gastroenterol Nutr. 2014 Apr;58(4):404-8

Trotter A, Stoll M, Leititis JU et al. Circadian variations of urinary electrolyte concentrations in preterm and term infants. J Pediatr 1996;128:253–256

Trotter A, Pohlandt F. Calcium and phosphorus retention in extremely preterm infants supplemented individually. Acta Paediatr 2002;91:1–4

**Evidence Level: III**

**How much of mineral and vitamin D to be supplemented?**

Breast milk Ca is absorbed at a rate of 70%, compared with 25%-30% for formula Ca. Lactose encourages absorption. Rigo et al reported the maximum retention of Ca (91 mg/kg/day) and higher bone accretion at discharge in 9 preterm infants who received breast milk with a fortifier containing 170 mg/kg/day of highly soluble Ca glycerophosphate. Rigo et al recommended administering 100-160 mg/kg/day of highly bioavailable Ca salts with 60-90 mg/kg/day of P and 800-1000 IU/day of vitamin D. The European Society of Paediatric Gastroenterology, Hepatology, and Nutrition's Committee on Nutrition advises a Ca intake of 120-140 mg/kg/day.

Carrascosa A, Gussiny_eM, Yeste D. Bone mass, osteopenia and osteoporosis. In: Argente J, Carrascosa A, Gracia R, Rodr_ıguez-Hierro F, eds. Treaty of pediatric and adolescent Endocrinology. 2nd ed. Barcelona, Spain: Doyma; 2000. p. 1353-82. (in Spanish)

ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010;50:85-91

Rigo J, De Curtis M, Pieltain C et al. Bone mineral metabolism in the micropremie. Clin Perinatol 2000;27:147-70

Rigo J, Pieltain C, Salle B, Senterre J. Enteral calcium, phosphate and vitamin D requirements and bone mineralization in preterm infants. Acta Paediatr 2007;96:969-74

**Evidence Level: IV**

**Does daily passive exercising help to prevent metabolic bone disease?**

Systematic reviews from 2016 (Stalnaker) and 2014 (Schulzke) have concluded that existing evidence from RCTs suggests that daily physical activity programs might promote short-term weight gain and bone mineralization in preterm infants. The meta-analysis by Schulzke demonstrated a positive effect of on daily weight gain (weighted mean difference (WMD) 2.21 g/kg/d, 95% confidence interval (CI) 1.23 to 3.19). Data also showed a positive effect on linear growth (WMD 0.12 cm/wk, 95% CI 0.01 to 0.24) but not on head growth (WMD -0.03 cm/wk, 95% CI -0.14 to 0.08) during the study period. Both reviews however highlight that existing RCTs are too small and with too short a follow up (making risks harder to identify) to make a confident recommendation for clinical practice.

Schulzke SM, Kaempfen S, Trachsel D et al. Physical activity programs for promoting bone mineralization and growth in preterm infants. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD005387 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005387.pub3/full

Stalnaker KA, Poskey GA. Osteopenia of Prematurity: Does Physical Activity Improve Bone Mineralization in Preterm Infants? Neonatal Netw. 2016;35:95-104

**Last amended July 2019**
**Last reviews September 2021**