INTRODUCTION

Metabolic bone disease of prematurity (MBDP) refers to the skeletal demineralisation that occurs in preterm infants. The main cause of MBDP is inadequate mineral (calcium and phosphorus) accretion in the skeleton, as 80% of total foetal bone mineral accretion occurs in the third trimester, and the inability of postnatal feeding regimens to match the intrauterine mineral accretion rate.\(^1\)\(^-\)\(^3\)

With the introduction of breast milk fortification and specific preterm formulae (which both provide extra calcium and phosphorus...
mineral), the incidence of MBDP has decreased over the decades.\(^4,5\)

Although guidance exists for the risk factors and nutritional preventative strategies for MBDP,\(^6,8\) there are no consensus guidelines regarding the screening, diagnosis, treatment or monitoring of MBDP. Investigations for screening and diagnosis are important, as MBDP is largely a clinically asymptomatic condition until late into the disease process, and therefore, biochemical markers or radiographs usually suggest the disease. If left untreated, pathological fractures can occur.

The authors have noted recent anecdotal cases with pathological fractures and severe secondary hyperparathyroidism, arising from inorganic phosphate supplementation without concomitant administration of calcium supplements. The management of these cases appears to neglect some of the pathophysiological basis of secondary hyperparathyroidism and its sequelae, which arise from inappropriate treatment of MBDP with phosphate supplements alone.\(^9\)

Thus, we conducted a survey of neonatologists across the United Kingdom (UK) to establish their current practices regarding prevention, screening, diagnosis, treatment and monitoring of MBDP. At the same time, an equivalent survey was conducted nationally amongst paediatric endocrinologists who manage children with metabolic bone disorders. These individuals are consulted by neonatal teams for advice on management of MBDP and allow comparison of responses between the two groups.

2 | METHODS

A survey consisting of eleven questions plus an area for free-text comments was designed and uploaded on to SurveyMonkey\(^®\) (https://www.surveymonkey.com; Appendix S1). Most questions required selection of the option(s) that applied, but a 5-point Likert scale was used to gauge the relative importance of screening and diagnostic investigations (‘not important’, ‘slightly important’, ‘moderately important’, ‘important’, ‘essential’). The link for the survey and a request for dissemination within their neonatal network were sent to the neonatal network clinical leads of the 20 neonatal networks listed with the British Association of Perinatal Medicine (BAPM, https://www.bapm.org/neonatal-networks). This meant distribution to all 194 neonatal units (ranging from district general hospitals with special care baby units, through to tertiary neonatal intensive care units) across the UK (England, Scotland, Wales and Northern Ireland) could be achieved.

A similar survey consisting of nine questions was designed and uploaded on to SurveyMonkey\(^®\) for completion by paediatric endocrinologists with an interest in the management of disorders of bone and mineral metabolism (Appendix S2). The link for this survey and request for completion were disseminated to 19 such paediatric endocrinology consultants located across the 11 paediatric centres across the UK who regularly provide tertiary advice for children with metabolic bone disorders.

The surveys were open for 7 weeks for completion, with data analysed thereafter. With reference to responses to the Likert scale for importance of screening and diagnostic investigations, as responses to each investigation were not mandatory, no response was considered to represent a ‘not important’ answer. Numbers were allocated to the Likert scale (‘not important’ = 1, ‘slightly important’ = 2, ‘moderately important’ = 3, ‘important’ = 4, ‘essential’ = 5), with weighted averages calculated by multiplying each of these numerical scores by the number of responders, taking the sum of these and dividing by the total number of responders. Therefore, a minimum weighted average would be 1.0, whereby all responders selected the ‘not important’ option to that question; and the maximum weighted average would be 5.0, whereby all responders selected the ‘essential’ response to that question. Statistical analysis to compare between neonatal and endocrine responses was using two-tailed Fishers’ test for qualitative variables, with percentages used to report frequency of selections. For quantitative variables (ie weighted averages), the two-tailed Mann-Whitney \(U\) test was used as the data were not normally distributed.

As the study was a survey on healthcare provision and did not collect individual patient information, research ethics approval was not required.

3 | RESULTS

3.1 | Responders

Sixty-nine individuals responded to the neonatal survey, from 53 neonatal units out of 194 neonatal units in the UK (response rate 27%). The location of responders across the UK indicated an even geographical distribution (Figure 1). Many free-text comments reported the lack of consensus guidelines creating confusion in the optimal management of MBDP.

Fifteen individuals responded to the endocrine survey. However, two responses were excluded as they were from a radiologist and a neonatologist; therefore, 13 responses were analysed (response rate 68%).

| Key Notes |
| --- |
| • Metabolic bone disease of prematurity is characterised by poor mineralisation of the preterm skeleton due to suboptimal accrual of calcium and phosphorus mineral. |
| • This nationwide electronic survey demonstrates that plasma parathyroid hormone level is under-utilised by neonatologists as an investigation for screening, diagnosis and guiding management. |
| • Phosphate supplements appear to be used almost universally for treatment by neonatologists, with much less emphasis on calcium supplementation. |
3.2 | Screening groups

The commonest criteria used by neonatal responders for undertaking screening for MBDP are gestational age below 32 weeks (59%) and a birthweight below 1500 g (48%) (Figure 2). Other risk factors that commonly initiate screening for MBDP include parenteral nutrition (39%), diuretic use (28%), chronic lung disease (25%) and steroid use (23%). Lack of specific screening criteria was reported by 13% of neonatal responders.

3.3 | Prophylaxis

When considering prophylactic treatments given routinely to prevent the development of MBDP in at-risk neonates, the most commonly utilised by neonatal responders are multivitamin supplements (90%) and phosphate supplements (54%) (Table 1). Calcium supplements were used by 4 (6%) individuals and alfacalcidol (1-hydroxycalciferol—an active vitamin D analogue) by 5 (7%). The results were not significantly different statistically for endocrine responders.

3.4 | Screening investigations

The two screening investigations for MBDP considered most important by neonatal responders were serum alkaline phosphatase (ALP) and serum phosphate, with weighted averages of 4.6 (SD 0.6) and 4.5 (SD 0.9), respectively (Figure 3). Identical weighted averages were also obtained for these two investigations as screening tests in the endocrine survey.

The remainder of investigations for screening (except serum calcium) were largely considered ‘not important’ or ‘slightly important’ by neonatal responders, with weighted averages of 1.3–1.7. In contrast, endocrine responders placed significantly greater emphasis on plasma parathyroid hormone (PTH) (weighted average 4.1 [SD 1.2] vs. 1.7 [SD 1.0], \( p < 0.001 \)), 25-hydroxyvitamin D (weighted average 3.3 [SD 1.5] vs. 1.6 [SD 1.0], \( p < 0.001 \)) and urine tubular reabsorption of phosphate (weighted average 2.2 [SD 1.2] vs. 1.3 [SD 0.8], \( p < 0.001 \)).

3.5 | Diagnostic investigations

Similar to findings with screening investigations, high serum ALP and low serum phosphate were felt to be the most important investigations in diagnosing MBDP by neonatal responders, with weighted averages of 4.4 (SD 0.9) and 4.1 (SD 1.1), respectively (Figure 4). As well as low serum phosphate and high serum ALP, endocrine responders placed significantly greater emphasis on raised plasma PTH (weighted average 4.2 [SD 1.0] vs. 1.9 [SD 1.3], \( p < 0.001 \)), low 25-hydroxyvitamin D (weighted average 3.1 [SD 1.2] vs. 1.7 [SD 1.1], \( p < 0.001 \)) and radiograph changes (weighted average 3.6 [SD 1.2] vs. 2.3 [SD 1.4], \( p = 0.002 \)).

3.6 | Treatments

Sixty-eight (99%) of 69 neonatal responders used phosphate supplements as treatment for MBDP (Table 2). Calcium supplements and alfacalcidol were used by 19 (28%) and 34 (49%) of neonatal responders, respectively. Although there appeared to be greater calcium supplement use (54%) and lower alfacalcidol use (23%), the only statistically significant difference amongst endocrine responders was of lower phosphate supplement use (62%, \( p < 0.001 \)).

3.7 | Monitoring investigations

Serum ALP (97%) and phosphate (94%) were almost universally used by neonatal responders to monitor response of MBDP to treatment, with plasma PTH (4%) and radiograph changes (4%) rarely used (Table 3). In contrast, although many endocrine responders utilise serum ALP (92%) and phosphate (77%), they also relied strongly on plasma PTH (85%, \( p < 0.001 \)) and radiograph changes (54%, \( p < 0.001 \)).
To the best of our knowledge, this is the first national survey of MBDP practices in the UK for over 10 years. Much like the survey in 2008, this current survey demonstrates ongoing practices of focusing on serum levels of ALP, phosphate and calcium for screening and diagnosis; weekly screening investigations; and treatment almost universally based on phosphate supplementation.\textsuperscript{10}

The only other national survey of practice was from the United States of America.\textsuperscript{11} It replicated this current survey’s findings of gestational age and birthweight being the commonest factors determining screening.\textsuperscript{11} But in contrast to our findings, a gestational
age of <28 weeks and birthweight of less than 1000 g were the commonest thresholds for screening.

The gestational and birthweight thresholds most commonly employed by neonatologists in our survey for screening for MBDP were 32 weeks and 1500 g, respectively. The American Academy of Pediatrics guideline suggests that being <28 weeks of gestation and <1000 g at birth puts a neonate at high-risk for MBDP. However, it also states that at birthweights >1500 g, MBDP is rarely seen. Such a thought process may explain the disparity in practices in our survey and the American survey. Furthermore, as maximal in utero bone mineral accretion occurs from 32 weeks gestation, this may explain the rationale for employing 32 weeks as the gestational threshold to implement screening for MBDP.

Similar to other surveys, and indeed the authors’ observations in clinical practice, most neonatologists place greatest (and almost exclusive) emphasis on serum ALP and phosphate levels in screening, diagnosing and monitoring MBDP. A systematic review has demonstrated that there is no single biochemical marker that is diagnostic of MBDP. However, the older studies on which this is based have failed to investigate the potential value of plasma PTH as a marker for MBDP, presumably as reliable PTH assays were not as readily available in the past. More recently, Moreira et al have demonstrated that raised plasma PTH is more sensitive, and as specific, as raised ALP in diagnosing severe MBDP. Furthermore, plasma PTH is also a useful investigation for monitoring response. However, our survey demonstrates a low importance placed on plasma PTH for screening and diagnosis by neonatal responders, and only 4% utilising it for monitoring. This is in marked contrast to endocrine responders, who use this much more frequently for screening, diagnosis and monitoring. This may partly be explained by the fact that tertiary paediatric endocrinologists are only contacted about cases of MBDP that are severe, not responsive to ‘standard’ treatment or demonstrate hyperparathyroidism when measured. On the other hand, paediatric endocrinologists may be basing their investigations on the hormonal pathophysiology underlying MBDP, as described below, and elsewhere in greater detail.

It is recognised that MBDP is due to a deficiency in both calcium and phosphorus mineral accretion, and therefore, guidance is

![Screening investigation](image-url)
focused on administering adequate levels of both minerals, as well
as vitamin D, through enteral and parenteral feeds\textsuperscript{6-16,17} (Table S1).
Whereas a low serum phosphate would imply phosphate deficiency
as the aetiology, in fact low serum phosphate as well as raised
serum ALP is universal to MBDP, regardless of whether calcium or
phosphate deficiency predominates (as described in greater detail
elsewhere\textsuperscript{9}). This is because raised plasma PTH, in response to cal-
cium deficiency to maintain normal serum calcium concentration,
will drive bone demineralisation (resulting in elevated serum ALP)
and renal phosphate excretion (resulting in low serum phosphate).

\textbf{FIGURE 4}  Weighted averages of neonatal ($N = 69$) and endocrine ($N = 13$) responders for the importance of each investigation in
\textbf{diagnosis of MBDP (1 = not important through to 5 = essential). Statistical comparison between the weighted averages of the two groups of
responders was performed using the two-tailed Mann-Whitney $U$ test, with error bars representing the standard deviation of each weighted average. *$p < 0.001$; **$p < 0.01$. 1,25-OHD, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; Ca:Cr ratio, calcium-to-creatinine ratio; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphates.}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Treatment & Percentage of neonatal responders & Percentage of endocrine responders & $p$-value \\
\hline
Phosphate supplements & 99 & 62 & <0.001 \\
Calcium supplements & 28 & 54 & 0.10 \\
Alfacalcidol & 49 & 23 & 0.13 \\
Multivitamins/vitamin D supplements & 78 & 85 & 1.00 \\
Physiotherapy & 6 & 0 & 1.00 \\
\hline
\end{tabular}
\caption{Percentage of neonatal ($N = 69$) and endocrine ($N = 13$) responders that would use each treatment for managing MBDP}
\end{table}

\textbf{Note: More than one treatment could be selected by each responder. Statistical comparison between the percentages of the two groups of responders was performed using the two-tailed Fisher's test. Bold value indicates $p$-values that are statistically significant ($<0.05$).}
Ironing hyperparathyroidism. This is important to consider prior to treatment strategies. Similar to the survey by Harrison et al., phosphate supplementation appears the ‘standard’ treatment, but with only 28% using calcium supplementation to treat MBDP. On the other hand, the literature reports that enteral calcium-to-phosphorus ratios should be maintained at 1.5:1–1.7:1 on a mg to mg basis for optimal absorption and retention. This would imply that calcium deficiency is very common in MBDP, and is recognised in the survey of American neonatal practices. In such cases, phosphate supplementation may actually worsen the clinical picture, by further exacerbating hyperparathyroidism. This is important to consider prior to prescribing phosphate supplementation, to avoid hyperparathyroidism by monitoring PTH and considering concurrent (or even isolated) calcium supplementation depending on aetiology and optimal calcium-to-phosphorus intake ratios. Consideration of underlying pathophysiology is even more relevant with regard to phosphate supplementation as prophylaxis to prevent MBDP (as 54% of the neonatal responders do), for which no evidence of efficacy exists in the first place.

Similar to the survey by Kelly et al., we demonstrate that active vitamin D analogues (such as alfacalcidol and calcitriol—1,25-dihydroxycholecalciferol) are part of current treatment practices for MBDP—49% of neonatal responders and even 23% of endocrine responders use this. This is surprising, as there is no literature to support efficacy or rationale. It may be historically driven, with concerns about immaturity of 25-hydroxylation in preterm infants. However, this has long been demonstrated not to be the case.

This survey comes with its own limitations. The response rate meant that responses were only obtained from 27% of neonatal units; thus, it may not be truly reflective of current practices. Furthermore, although neonatologists from all neonatal units should have been contacted, only those that are interested in MBDP or feel strongly about its management may have responded, creating a biased reflection of current practice. However, given the even distribution across the UK, and in keeping with our observations, we feel these responses are reflective of current neonatal practices. The nature of an online survey is such that focused responses are requested, which does not fully appreciate the subtleties of approach employed by each responder. Although free-text comments were available, this may not have been utilised fully. Finally, comparison of results between two groups (neonatal and endocrine responders) may be affected by the fact that they may encounter different spectrums of disease.

This survey has highlighted the need for an evidence-based consensus guideline for the management of MBDP to standardise safe and effective practice. Further research is required to facilitate this. This includes identifying through prospective studies in preterm neonates the sensitivity and specificity of various biochemical parameters (such as serum ALP and phosphate, plasma PTH and urine tubular reabsorption of phosphate) in screening of MBDP. Prior to that, studies that can establish normative reference ranges for plasma PTH and urine tubular reabsorption of phosphate specifically in preterm neonates are required for greater understanding of these parameters. Finally, prospective trials of differing calcium-to-phosphorus intake ratios will also help clarify whether the optimal ratios identified previously are applicable clinically also in managing MBDP.

### Table 3: Percentage of neonatal and endocrine responders that would use each investigation in monitoring the resolution/progression of metabolic bone disease of prematurity following diagnosis

| Monitoring investigation | Percentage of neonatal responders | Percentage of endocrine responders | p-value |
|--------------------------|-----------------------------------|-----------------------------------|---------|
| Serum calcium            | 58                                | 69                                | 0.55    |
| Serum phosphate          | 93                                | 77                                | 0.11    |
| Serum ALP                | 97                                | 92                                | 0.41    |
| Plasma PTH               | 4                                 | 85                                | <0.001  |
| Radiograph of wrist/knee | 4                                 | 54                                | <0.001  |
| Urine excretion studies  | 7                                 | 8                                 | 1.00    |

Note: More than one treatment could be selected by each responder. Statistical comparison between the percentages of the two groups of responders was performed using the two-tailed Fishers’ test. Bold values indicate p-values that are statistically significant (<0.05).

Abbreviations: ALP, alkaline phosphatase; PTH, parathyroid hormone.
Alfacalcidol treatment for MBDP also appears to have become routine practice, with no evidence of its efficacy in the literature or any pathophysiological rationale underlying its use. Prospective studies underpinning evidence-based consensus guidelines are required to standardise safe and effective screening and management of MBDP across the UK.

ACKNOWLEDGEMENTS
We would like to thank Mr Syed Jilani (Information Manager, Royal Manchester Children’s Hospital) for assistance with designing and uploading the surveys and BAPM neonatal network clinical leads for distributing the surveys within their regions.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare relevant to this manuscript.

ORCID
Amish Chinoy https://orcid.org/0000-0002-8991-1614

REFERENCES
1. Ellis KJ, Shypailo RJ, Schanler RJ. Body composition of the preterm infant. Ann Hum Biol. 1994;21(6):533-545.
2. Greer FR. Osteopenia of prematurity. Annu Rev Nutr. 1994;14:169-185.
3. Ziegler EE, O’Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth. 1976;40(4):329-341.
4. Lyon AJ, McIntosh N, Wheeler K, Williams JE. Radiological rickets in extremely low birthweight infants. Pediatr Radiol. 1987;17(1):56-58.
5. Mitchell SM, Rogers SP, Hicks PD, Hawthorne KM, Parker BR, Abrams SA. High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support. BMC Pediatr. 2009;9:47.
6. Abrams SA. Committee on Nutrition. Calcium and vitamin d requirements of enterally fed preterm infants. Pediatrics. 2013;131(5):e1676-e1686.
7. Agostoni C, Buonocore G, Carnielli VP, et al. 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(1):85-91.
8. Koletzko B, PoinDEXter B, Uauy R. Nutritional care of preterm infants: scientific basis and practical guidelines; 2014.
9. Chinoy A, Mughal MZ, Padidela R. Metabolic bone disease of prematurity: causes, recognition, prevention, treatment and long-term consequences. Arch Dis Child Fetal Neonatal Ed. 2019;104(5):F560-F566.
10. Harrison CM, Johnson K, McKechnie E. Osteopenia of prematurity: a national survey and review of practice. Acta Paediatr. 2008;97(4):407-413.
11. Kelly A, Kovatch KJ, Garber SJ. Metabolic bone disease screening practices among U.S. neonatologists. Clin Pediatr. 2014;53(11):1077-1083.
12. Visser F, Sprij AJ, Brus F. The validity of biochemical markers in metabolic bone disease in preterm infants: a systematic review. Acta Paediatr. 2012;101(6):562-568.
13. Moreira A, Swischuk L, Malloy M, Mudd D, Blanco C, Geary C. Parathyroid hormone as a marker for metabolic bone disease of prematurity. J Perinatol. 2014;34(10):787-791.
14. Moreira A, February M, Geary C. Parathyroid hormone levels in neonates with suspected osteopenia. J Paediatr Child Health. 2013;49(1):E12-E16.
15. Rayannavar A, Calabria AC. Screening for metabolic bone disease of prematurity. Semin Fetal Neonatal Med. 2020;25(1):101086.
16. Mihatsch W, Fewtrell M, Goulet O, et al. ESPGHAN/ESPR/ESPEP guidelines on pediatric parenteral nutrition: calcium, phosphorus and magnesium. Clin Nutr. 2018;37(6 Pt B):2360-2365.
17. Nehra D, Carlson SJ, Fallon EM, et al. A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for metabolic bone disease. J Parenter Enteral Nutr. 2013;37(5):570-598.
18. Robinson MJ, Merrett AL, Tetlow VA, Compston JE. Plasma 25-hydroxyvitamin D concentrations in preterm infants receiving oral vitamin D supplements. Arch Dis Child. 1981;56(2):144-145.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Chinoy A, Mughal MZ, Padidela R. Metabolic bone disease of prematurity—National survey of current neonatal and paediatric endocrine approaches. Acta Paediatr. 2021;110:1855-1862. https://doi.org/10.1111/apa.15654.