

REGULAR ARTICLE

Metabolic bone disease of prematurity—National survey of current neonatal and paediatric endocrine approaches

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Abstract

Aim: This study aimed to identify current trends in the management of metabolic bone disease of prematurity (MBDP) in the United Kingdom.

Methods: A nationwide electronic survey was disseminated to all neonatal networks across the United Kingdom, as well as to paediatric endocrinologists for comparison. Weighted averages were used to compare relative importance placed on screening and diagnostic investigations (1 = not important, 5 = essential).

Results: Sixty-nine individuals responded from 53 neonatal units. Greatest emphasis was placed on levels of serum phosphate and alkaline phosphatase for screening (weighted average 4.5 and 4.6, respectively), diagnosis (weighted average 4.1 and 4.5, respectively) and monitoring (93% and 97% of neonatal responders, respectively) of MBDP by neonatologists. Although similar results were obtained for endocrinologists, significantly greater emphasis was placed on plasma parathyroid hormone (PTH) level for screening, diagnosis and monitoring ($p < 0.001$ for each). Phosphate supplementation was reported almost universally by neonatal responders (99%), but was significantly less for endocrine responders (62%) for the treatment of MBDP ($p < 0.001$).

Conclusion: There is an under-utilisation of plasma PTH as a screening, diagnostic and monitoring investigation to guide appropriate supplementation for MBDP by neonatologists.

KEYWORDS

calcium, parathyroid hormone, phosphate

1 | 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

Abbreviations: 1,25-OHD, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; BAPM, British Association of Perinatal Medicine; Ca, calcium; Ca:Cr, calcium-to-creatinine ratio; CaSR, calcium-sensing receptor; MBDP, metabolic bone disease of prematurity; PO₄, phosphate; PTH, parathyroid hormone; SD, standard deviation; TRP, tubular reabsorption of phosphate; UK, United Kingdom.

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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

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.

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%).



FIGURE 1 Pictorial representation of the 53 neonatal units across the United Kingdom that provided responses to the survey

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 initiates 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-hydroxycholecalciferol—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%, $p < 0.001$).

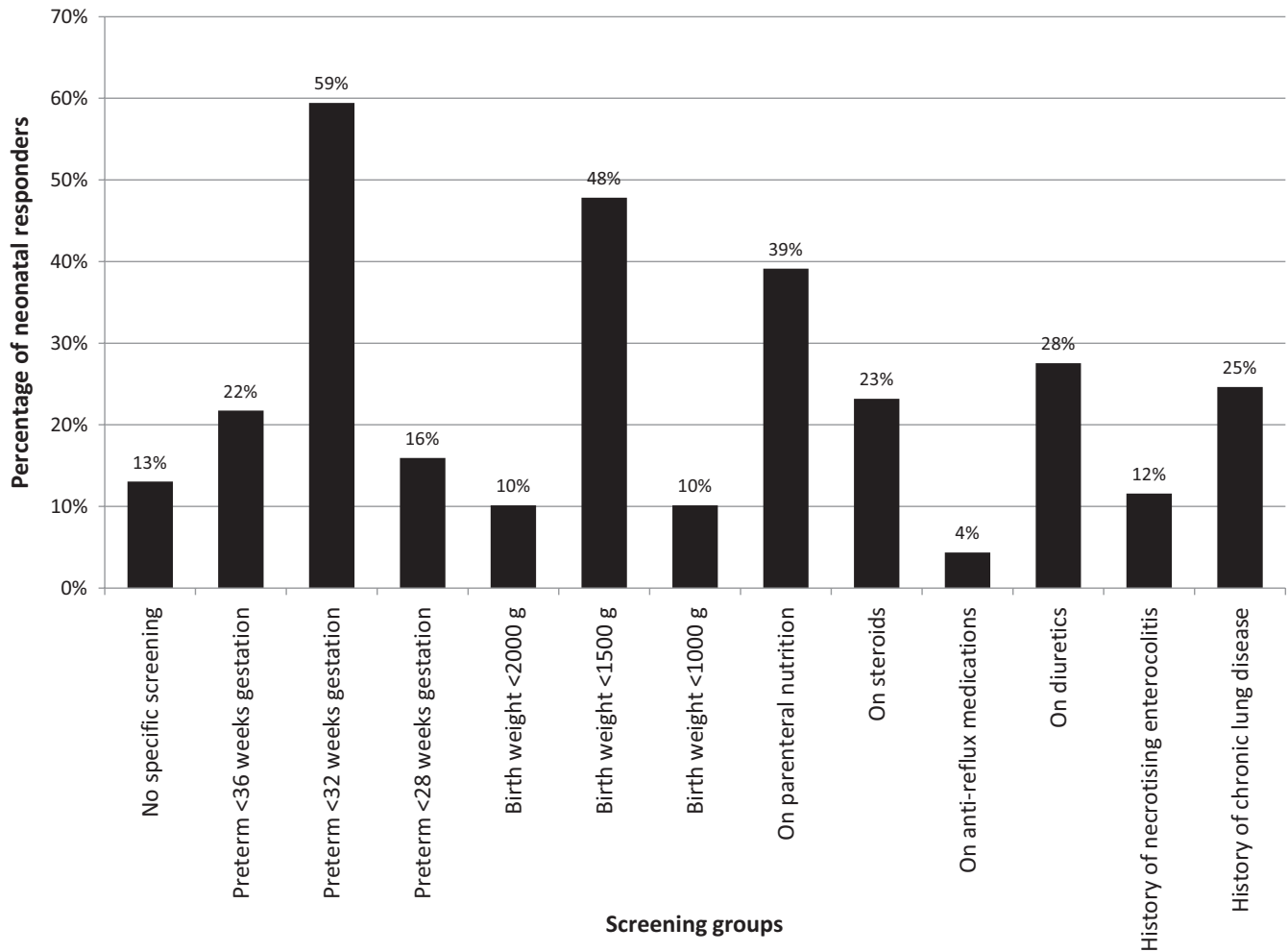


FIGURE 2 Percentage of neonatal responders ($N = 69$) that selected each infant group for screening for MBDP. More than one group could be selected by each responder

Prophylactic treatment	Percentage of neonatal responders	Percentage of endocrine responders	p -value
Phosphate supplements	54	23	0.07
Calcium supplements	6	23	0.08
Multivitamin supplements	90	69	0.07
Vitamin D supplements	17	8	0.68
Alfacalcidol	7	0	1.00
Physiotherapy	7	0	1.00
None	1	8	0.29

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.

TABLE 1 Percentage of neonatal ($N = 69$) and endocrine ($N = 13$) responders that would routinely give each prophylactic treatment to prevent the development of MBDP in at-risk infants

4 | DISCUSSION

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.¹⁰

The only other national survey of practice was from the United States of America.¹¹ It replicated this current survey's findings of gestational age and birthweight being the commonest factors determining screening.¹¹ But in contrast to our findings, a gestational

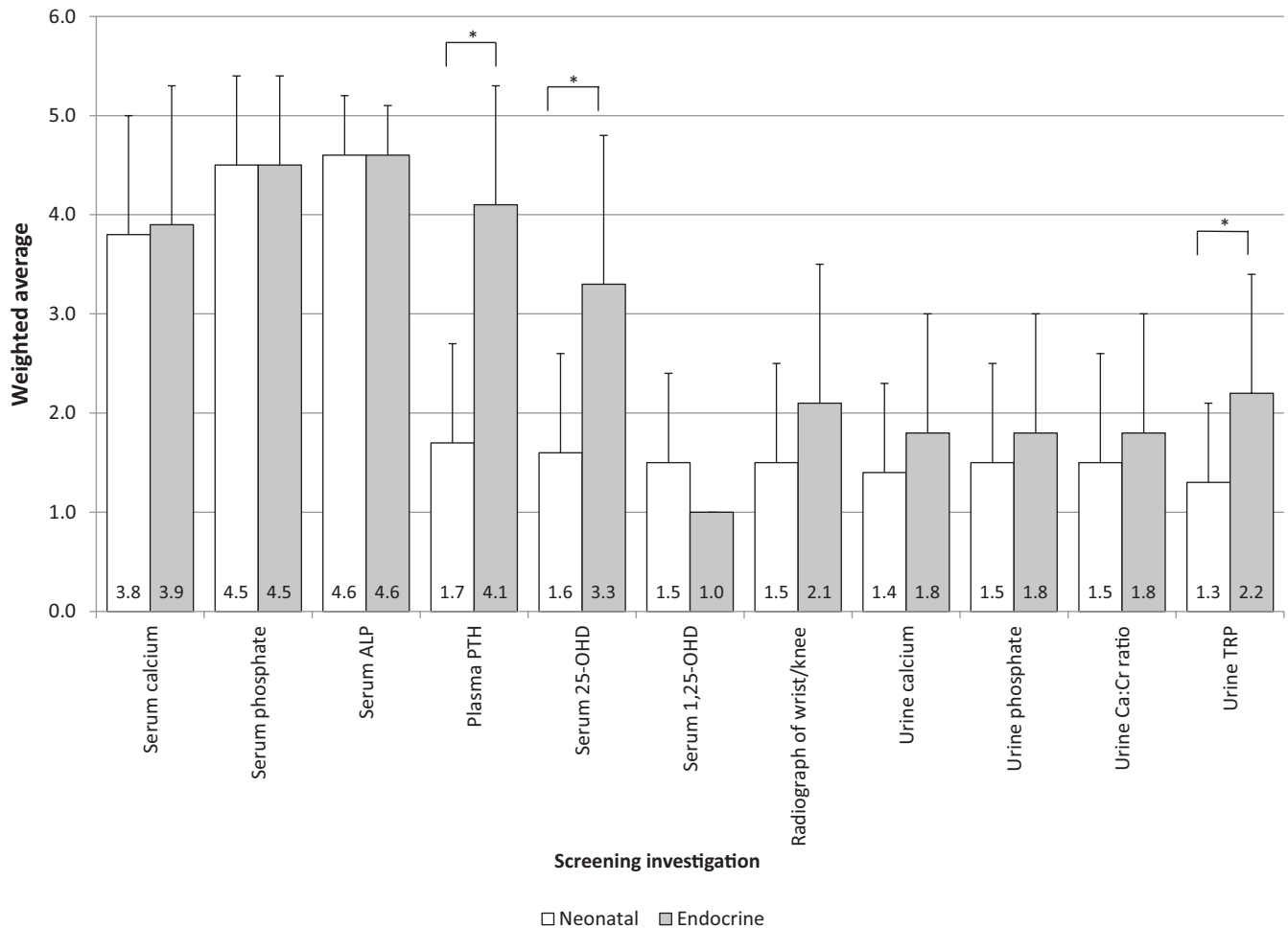


FIGURE 3 Weighted averages of neonatal ($N = 69$) and endocrine ($N = 13$) responders for the importance of each investigation in screening for MBDP (1 = not important through to 5 = essential). Statistical comparison between the weighted averages of the two groups of responders was performed using the two-tailed Mann-Whitney U test, with error bars representing the standard deviation of each weighted average. * $p < 0.001$. 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 phosphate

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.⁶ 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,^{1,3} 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.¹² 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 al¹³ 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.¹⁴ 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.¹⁵

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

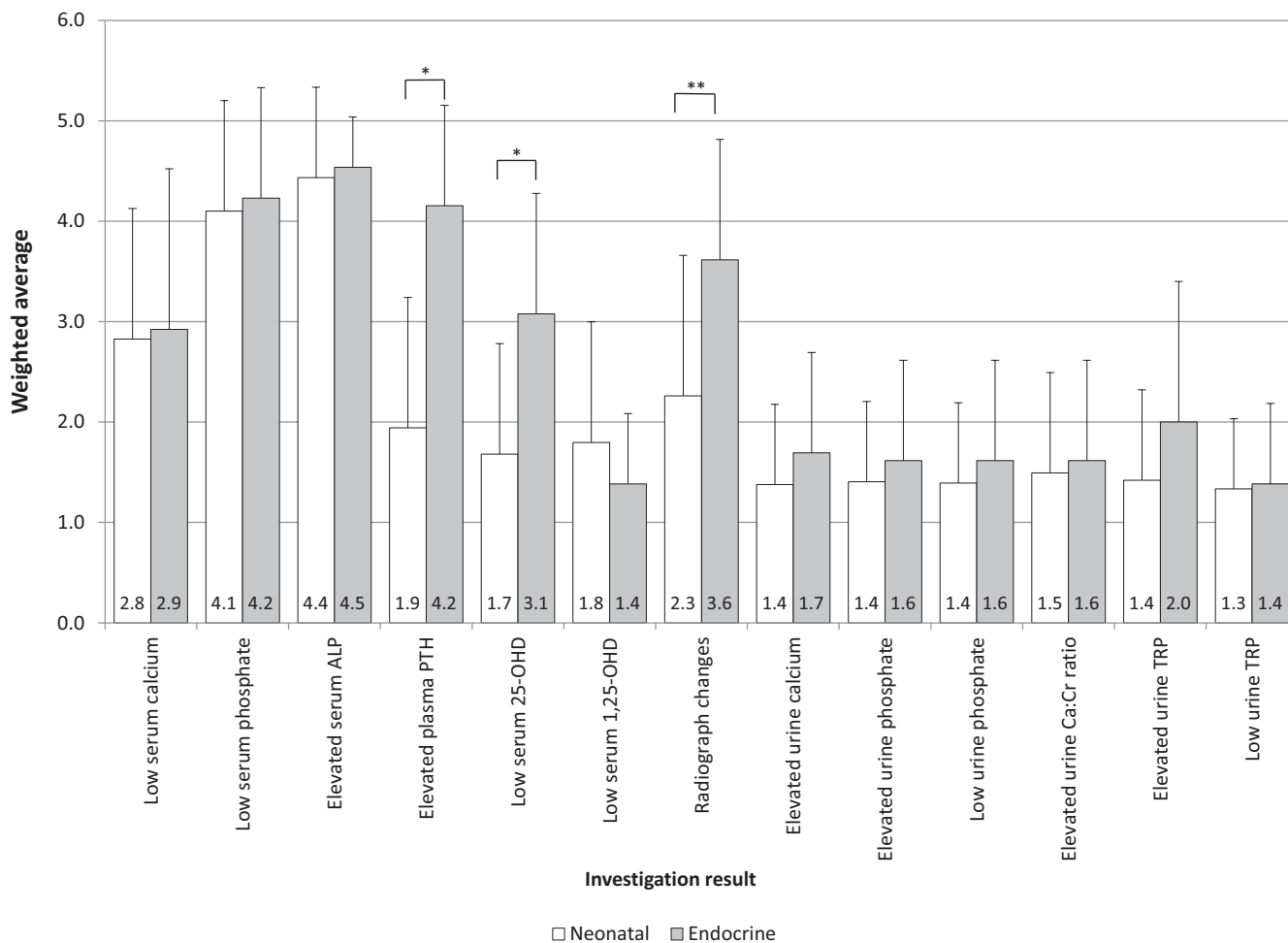


FIGURE 4 Weighted averages of neonatal ($N = 69$) and endocrine ($N = 13$) responders for the importance of each investigation in diagnosis of MBDP (1 = not important through to 5 = essential). Statistical comparison between the weighted averages of the two groups of responders was performed using the 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

Treatment	Percentage of neonatal responders	Percentage of endocrine responders	p -value
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

TABLE 2 Percentage of neonatal ($N = 69$) and endocrine ($N = 13$) responders that would use each treatment for managing MBDP

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 value indicates p -values that are statistically significant (<0.05).

focused on administering adequate levels of both minerals, as well as vitamin D, through enteral and parenteral feeds^{6-8,16,17} (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 elsewhere⁹). This is because raised plasma PTH, in response to calcium 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)

TABLE 3 Percentage of neonatal ($N = 69$) and endocrine ($N = 13$) 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.

(Figure S1). Thus, plasma PTH may serve as an earlier marker of MBDP and helps differentiate between predominantly calcium deficiency from predominantly phosphate deficiency, to guide appropriate treatment.

Although not specifically explored in our survey, the impression that phosphate deficiency primarily underlies the current neonatal approach to MBDP management in the UK is suggested by treatment strategies. Similar to the survey by Harrison et al,¹⁰ 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 basis⁶ 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.¹¹ In such cases, phosphate supplementation may actually worsen the clinical picture, by further exacerbating hyperparathyroidism.⁹ 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.⁹ 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,¹¹ 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.¹⁸

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.

5 | CONCLUSION

Results of this survey have shown that neonatologists in the UK tend to use serum ALP and phosphate levels to screen, diagnose and monitor MBDP, and ubiquitously use phosphate supplements to treat MBDP. Such an approach implies phosphate deficiency is considered to be the only factor that is important in the aetiology of MBDP, neglecting the role of calcium deficiency. By under-utilising plasma PTH levels and calcium supplementation, one runs the risk of worsening MBDP by exacerbating secondary hyperparathyroidism.

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.

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CONFLICT OF INTEREST

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

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SUPPORTING INFORMATION

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

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