Article

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Long-Term Follow-up of Hypophosphatemic Bone Disease Associated With Elemental Formula Use: Sustained Correction of Bone Disease After Formula Change or Phosphate Supplementation

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Abstract

In this article, we describe the long-term outcomes of children who were previously reported to have developed hypophosphatemic bone disease in association with elemental formula use. An extended chart review allowed for an updated report of 34 children with regard to severity/duration of bone disease, extent of recovery, and time to correction using radiology reports and biochemical data. After implementation of formula change and/or phosphate supplementation, we found that serum phosphorus concentration increased and serum alkaline phosphatase activity decreased in all patients, normalizing by 6.6 ± 4.0 (mean ± SD) months following diagnosis. The decrease in serum alkaline phosphatase from diagnosis to the time of correction was moderately correlated with the concurrent increase in serum phosphorus ($R = 0.48$, $P < .05$). Age at diagnosis significantly correlated with time to resolution ($R = 0.51$, $P = .01$). This study supports the earlier report that bone disease associated with hypophosphatemia during elemental formula use responds to formula change and/or phosphate supplementation.

Keywords

nutrition, hypophosphatemia, rickets, phosphate bioavailability, amino acid–based elemental formula

Introduction

Clinical complications may occur with the use of amino acid–based elemental formula. We and others have previously reported that the use of such formulas in children with chronic disease, complex gastrointestinal conditions,[1-4] or congenital heart disease[5] can be associated with hypophosphatemic bone disease. The bone disease associated with such feeding has sometimes been mistaken for nonaccidental trauma.[6] Poor bioavailability of the phosphate in these formulas in certain children was proposed as the likely mechanism for hypophosphatemia, and treatment with phosphate salts or alternate formulas was generally recommended.[1] Initial follow-up of several of the reported cases suggested that these measures would adequately manage the problem over a 4- to 8-week period[1]; however, longer term evaluation of such children was not available at the time and has not been reported. Thus, our aim herein is to provide, by an extended chart review, the long-term clinical course in those initial cases where hypophosphatemic bone disease was documented. In that initial report, all identified children were receiving formula products as their sole source of nutrition; the 2 formulas usually identified were Neocate Infant (15, 29%) and

Neocate Junior (35, 69%). Bone disease was detected by low serum phosphorus levels for age and increased alkaline phosphatase levels. Collected radiographic reports described findings of fractures, rickets, osteopenia or decreased mineralization, bone disease, and gracile bones. This extended retrospective chart review of the available records from members of the original cohort provides further information regarding the long-term course of this hypophosphatemic bone disease and the potential for resolution with alternate feeding/supplementation regimens.

Methods

All patients included in this follow-up report were identified in the original study between 2015 and 2017 as having hypophosphatemia and bone disease associated with ingestion of amino acid–based formulas.[1] At the time of that report information was only available for the 4 to 8 weeks following intervention. Therefore, in the current study, we collected data for the maximum period of follow-up available at the time of review. This period varied across cases between 1 and 75 months after intervention, and thereby providing a more chronic picture of the effect of the intervention. After development of a data collection form, all centers/clinicians participating in the previous study were contacted regarding participation in this study and were requested to provide follow-up clinical information on the children originally described at their respective centers. After obtaining appropriate institutional review board approval (Yale University School of Medicine Human Investigation Committee; 000024776), investigators collected new descriptive details in 66% of the original cohort across 16 of the original 17 centers. All biochemical measurements were performed during clinical evaluations at the individual clinical centers and laboratories. All data were collected and shared in compliance with the ethics requirements of each center; given that this was a noninterventional chart review, consent from subjects' caregivers was not requested. After receipt of the supporting information for each case, data were collectively examined to identify severity and duration of bone disease, extent of recovery, time to correction, and potential correlates of time to resolution. The primary biochemical outcomes were serum phosphorus and serum alkaline phosphatase. Normalization of the serum alkaline phosphatase activity, the biochemical signature of osteomalacia and rickets, was considered to be the marker for biochemical resolution of bone disease and served to ascertain the reported "time to resolution." The time to resolution was defined by the time course between the time of initial diagnosis and the time of the first normal alkaline phosphatase level observed after implementation of therapeutic measures. Radiology as reported by the local clinical radiologists at each center were collected centrally and descriptive commentary regarding comparison of the skeletal changes at initial presentation and later time points were available for 24 patients (Supplementary Table, available online). Reports were categorized as either improved, corrected, or no change for analysis of

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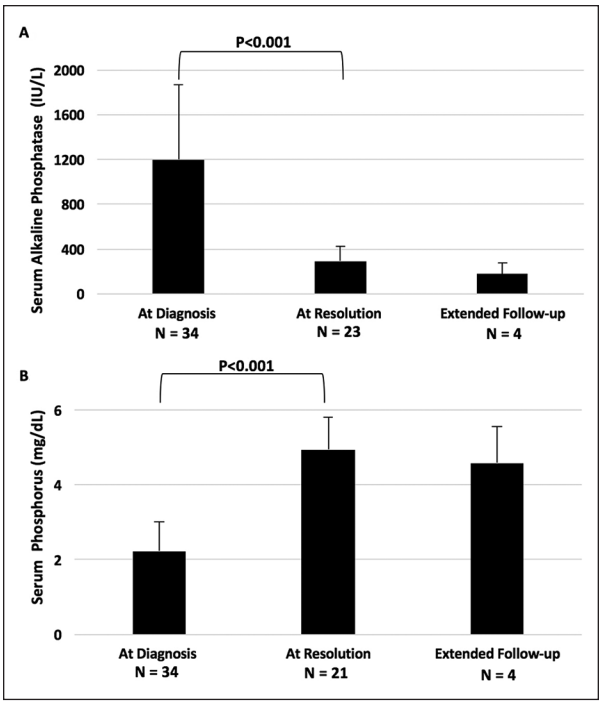

Figure 1. Biochemical changes with application of therapy and most recent values. (A) Mean (± SD) serum alkaline phosphatase at the time of diagnosis and before application of any therapeutic measures (first column), at the time of resolution of bone disease (second column), and extended data beyond resolution for 4 patients (third column). (B) Mean (± SD) serum phosphorus at the time of diagnosis and before application of any therapeutic measures (first column), at the time of resolution of bone disease as defined by normalization of alkaline phosphatase (second column), and extended data beyond resolution for 4 patients (third column). For both serum phosphorus and alkaline phosphatase, values at diagnosis were significantly different ($P < .001$) from those on resolution, while there was no difference between resolution and the extended follow-up in the 4 patients where data were available.

radiographic recovery. None of the cases were excluded because of the use of any particular formula product.

Results

We obtained data on 34 of the original 51 patients assessed in the original report (67%) (Supplementary Table). The mean age of children at the time of diagnosis was 3.4 ± 3.7 years, and mean age at the time of the patient's most recently available data was 6.7 ± 4.6 years. The serum phosphorus concentration at the time of diagnosis was 2.23 ± 0.77 mg/dL (median = 2.20 mg/dL), and serum alkaline phosphatase activity was 1200 ± 664 IU/L (median = 1022 IU/L; Figure 1). Radiographic evidence of skeletal disease at the time of diagnosis was present in 33/34 (97%), while in 1 patient exposure to formula was not of sufficient duration to result in clinical compromise of the skeleton. The mean duration of the follow-up period was 8.4 ± 4.9 months.

To manage the identified bone disease, 9 patients received a formula change as the only intervention, 8 received phosphate supplements as the sole treatment while remaining on the initial formula, and 17 underwent both a formula change and phosphate supplementation. Proton pump inhibitors were discontinued in 5 patients as part of treatment for hypophosphatemia. Serum phosphorus corrected rapidly with these interventions (usually within days), often occurring with concurrent hypocalcemia, as described in our original report.[1] In contrast, the time to biochemical resolution of disease (the interval between diagnosis and correction of serum alkaline phosphatase) was 6.6 ± 4.0 months for the entire group (median = 5 months), ranging from 1 to 17 months. Further follow-up data collected after biochemical resolution were available in 4 individuals, providing evidence that the biochemical resolution persisted for a mean of 34.0 ± 34.1 months (median = 30.5 months), without recurrence of disease in any case; the minimum and maximum times of follow-up for these cases were 8 and 75 months, respectively.

Figure 1A shows that mean serum alkaline phosphatase decreased to 291 ± 131 IU/L (median = 263 IU/L) at the time of biochemical resolution of bone disease. The mean decrease from baseline in serum alkaline phosphatase over this duration was 1013 ± 675 IU/L (median = 776 IU/L). Figure 1B shows that mean serum phosphorus values were within the normal range of 4.94 ± 0.88 mg/dL (median = 4.90 mg/dL) at the time of resolution, representing an increase of 2.52 ± 1.02 mg/dL (median = 2.50 mg/dL) from baseline. For both serum phosphorus and alkaline phosphatase, the mean values at this time were significantly different from those at baseline ($P < .001$). In the 4 cases with subsequent data from 8 to 75 months following the initial recorded resolution, the mean serum phosphorus level was 4.58 ± 0.99 mg/dL (median = 4.7 mg/dL) and the mean alkaline phosphatase level was 174 ± 105 IU/L (median = 158 IU/L). Thus, both serum phosphorus and alkaline phosphatase were maintained at levels comparable with that seen on resolution of disease (Figure 1). The magnitude of decrease in serum alkaline phosphatase level from diagnosis to resolution of bone disease was moderately correlated with the increase in serum phosphorus over this time ($R = 0.48$, $P = 0.027$; Figure 2).

The degree of radiographic improvement of skeletal lesions was based on available radiographs obtained at various intervals until skeletal disease was no longer suspected. The mean time interval between radiographs

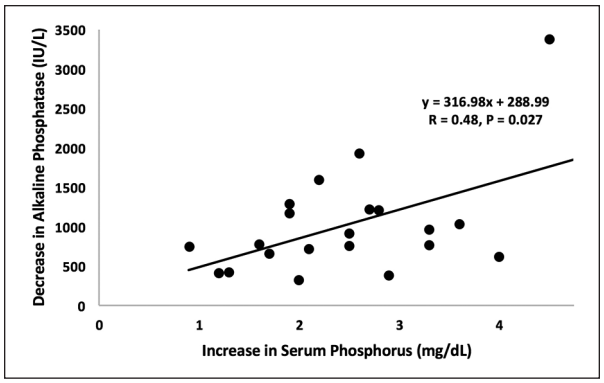

Figure 2. Relationship of increase in serum phosphorus to decrease in alkaline phosphatase. Pearson correlation of the increase in serum phosphorus between onset and resolution of disease (*x*-axis) and decrease in serum alkaline phosphatase over that time frame (*y*-axis). Increase in serum phosphorus is correlated with a decrease in alkaline phosphatase, despite the expected decreasing trend in serum phosphorus level as patients age ($R = 0.48$, $P = .027$). Per the equation shown (slope of regression line = 317), for each 1 mg/dL increase of serum phosphorus level, there was roughly a 317 IU/L decrease in serum alkaline phosphatase.

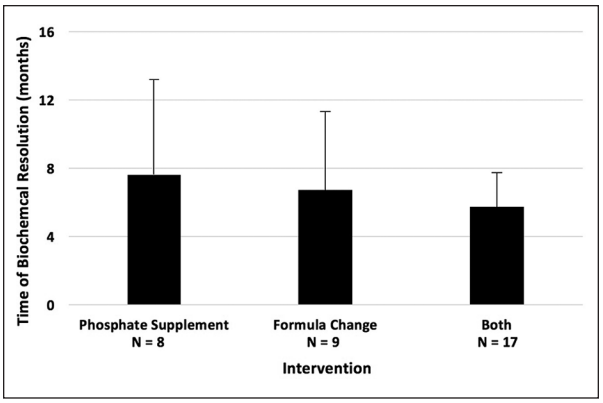

Figure 3. Relation of treatment to time course of biochemical resolution. Time to resolution after treatment with phosphate alone (first column, N = 8) was longer than with formula change alone (second column, N = 9) or after receiving both interventions combined (third column, N = 17). Column height and error bars represent mean with standard deviation. Biochemical resolution was defined as time to normalization of alkaline phosphatase levels.

was 7.6 ± 5.5 months (median = 5.8 months), ranging from 1 to 24 months. Of the 24 patients in whom follow-up radiographs were available, reports described 17 patients to have undergone radiographic correction of bone disease (71%), 6 with radiographic improvement (25%), and 1 patient was reported to have no change. No patient was reported to have worsening bone disease. Radiographs were obtained less frequently than biochemical data, and healing may have occurred more rapidly than the time between recorded radiographs.

Finally, we examined the potential correlates of the time to biochemical resolution. Time to resolution was not significantly correlated with either baseline serum phosphorus ($R = -0.17$, $P = .41$) or serum alkaline phosphatase ($R = 0.14$, $P = .52$); however, we found a significant correlation of time to resolution with age at the time of diagnosis ($R = 0.51$, $P = .01$). We also examined whether choice of intervention influenced the time to resolution (Figure 3). When only phosphate supplementation was employed, the mean time to resolution was 7.6 ± 5.6 months (median = 5.0 months). When formula change was employed, the mean time to resolution was 6.7 ± 4.6 months (median = 5.5 months) and if both were used mean time to resolution was 5.7 ± 2.0 months (median = 5.3 months). Although this trend suggested that a formula change was advantageous, there was no statistical difference among these groups (one-way analysis of variance; $P = .64$).

Discussion

This study provides further evidence for the association of Neocate amino acid–based formula use with hypophosphatemic bone disease. We show here that intervention with phosphate supplementation or alternate formula use is associated with long-term maintenance of normal serum phosphorus levels with correction of the primary biochemical marker of active rachitic disease, serum alkaline phosphatase. In keeping with the correction of serum biomarkers, nearly all available radiographic reports indicated improvement or normalization of bone disease. We also note, as in the initial description of these cases, that cases are most frequently observed in complex conditions requiring tube feeding or with underlying gastrointestinal disease. Indeed, Creo and others estimated that the frequency of hypophosphatemic bone disease in infants receiving Neocate formulas by enteral feeding tubes ranged from 11% to 23%.[2]

The positive response of the skeleton observed in this follow-up study is most likely due to the normalization of serum phosphorus, which when sustained over time, provides adequate mineral to the skeleton as to induce bone mineralization, thereby healing or improving the bone disease. The improved skeletal mineralization, in turn, resulted in correction of the alkaline phosphatase level, the biochemical hallmark of osteomalacia and rickets. We observed that younger patients experienced more rapid correction of bone disease, perhaps indicating that early identification allows for detection at a less severe stage, and thus more rapid restoration of normal

bone mineralization. Alternatively, it is possible that the younger skeleton is more responsive to corrections induced from increasing mineral supply due to greater rates of bone formation. Furthermore, we show that these corrective changes, with continued intervention, persisted in long-term follow-up. Other recent reports have recorded recovery patterns within months after formula change or phosphate supplementation. Dizygotic twins fed Neocate were thought to have hypophosphatemia because of maternal bisphosphonate exposure but corrected within 2 months following formula change.[7] One of the cases reported by Ali et al resolved within 3 months of formula change.[8]

During the current chart review, we recorded incidences of new cases of this phenomenon identified by the investigators, identifying 8 such cases, which is perhaps fewer than would be expected when compared with our initial report of 51 cases. However, the frequency of the problem in the United States may be changing with the recent reformulation of the formulas reported herein,[9] although reports in other regions (eg, Brazil) have continued, likely reflecting continued use of the earlier product.[3] Recently, 10 patients with hypophosphatemic rickets due to exclusive Neocate use were identified in the United Kingdom with normalization of biochemical findings and radiographical healing of rickets after formula discontinuation.[4]

The study is limited by a retrospective approach to chart review, and the associative analysis that such an approach necessitates. Nevertheless, the relatively large numbers of identified cases and persistent correction of serum phosphorus levels after intervention suggests bioavailability of phosphorus is suboptimal in such formula, particularly in the setting of complex/gastrointestinal disease or tube feeding. Our experience, combined with that of others, leads us to strongly advise that frequent monitoring of serum phosphorus (with alkaline phosphatase) levels be performed when using such formulas. Furthermore, correction of severe hypophosphatemia with either phosphate supplementation or alternate formula should be performed gradually, and should include monitoring of serum calcium and phosphorus levels as to avoid potential wide or rapid fluctuations of these minerals; coadministration of calcium and/or calcitriol may be necessary. The follow-up data reported here indicate that after an acute transition phase, resolution of disease is evident within approximately 7 months of formula change or phosphate supplementation, consistent with the limited reports available. Recurrence is unlikely if maintained on appropriate formula or supplementation. Future studies would be useful to identify specific mechanisms of phosphorus bioavailability in amino acid–based formulas.

Conclusion

Biochemical identification of hypophosphatemia and radiographic evidence of bone disease was found in patients receiving amino acid–based formulas (predominantly Neocate Infant and Neocate Junior) as their sole source of nutrition. All patients experienced a decrease in serum alkaline phosphatase and an increase in serum phosphorus after the intervention of either formula change, phosphate supplementation, or both, placing the majority of patients in expected biochemical ranges for their age. The decrease in serum alkaline phosphatase level from diagnosis to resolution of bone disease was moderately correlated with the increase in serum phosphorus over this time, and almost all subjects demonstrated improvement in bone disease during the reported observation period. Patients at younger ages and with earlier identification appeared to recover faster. Thus, formula change and/or phosphorus supplementation is effective in correcting and maintaining serum alkaline phosphatase and serum phosphorus levels over an extended course.

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Author Contributions

ASE and TOC contributed to conception and design of study, data acquisition, analysis, and interpretation; drafted and critically revised manuscript, and gave final approval for publication. NSM, LMW, PB, HW, DRW, LAD, EAI, JG, DC, PZ,

LST, SA, AC, PT, RF, RG and LC contributed to data acquisition, critical revision of manuscript, and gave final approval for publication.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Carpenter has received consulting fees from Nutricia. The other authors have no conflicts of interest to disclose.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Gonzalez-Ballesteros LF, Ma NS, Gordon RJ, et al. Unexpected widespread hypophosphatemia and bone disease associated with elemental formula use in infants and children. *Bone*. 2017;97:287-292.
2. Creo AL, Epp LM, Buchholtz JA, Tebben PJ. Prevalence of metabolic bone disease in tube-fed children receiving elemental formula. *Horm Res Paediatr*. 2018;90:291-298.
3. Silva FD, Ferreirz TL, de Melo NV, Valadao GFC, Albuquerque CTM. Raquitismo hipofosfatemico relacionado ao uso de Neocate: relato de tres casos. Paper presented at: 13th COBRAPEM (Congresso Brasileiro Pediatrico de Endocrinologia e Metabologia); May 29, 2019; Costa do Sauipe, Brasil.
4. Uday S, Sakka S, Davies J, et al. Elemental formula associated hypophosphataemic rickets. *Clin Nutr*. 2019;38:2246-2250.
5. Marino LV, Venkatesh P, Ho A, Beattie RM, Bharucha T. Hypophosphataemia in infants with CHD treated with amino acid infant formula. *Cardiol Young*. 2018;28:1370-1374.
6. Abulebda K, Abu-Sultaneh S, Lutfi R. It is not always child abuse: multiple fractures due to hypophosphatemic rickets associated with elemental formula use. *Clin Case Rep*. 2017;5:1348-1351.
7. Gerin M, Jambon G, Fouque-Aubert A, et al. Neonatal transient hypophosphatemic hypercalciuric rickets in dizygous twins: a role for maternal alendronate therapy before pregnancy or antireflux medications? *Arch Pediatr*. 2016;23:957-962.
8. Ali SA, Mathalikunnel A, Bhardwaj V, Braskett M, Pitukcheewanont P. Nutritional hypophosphatemic rickets secondary to Neocate® use. *Osteoporosis Int*. 2019;30:1887-1891.
9. Upgraded Neocate Junior. Neocate syneo. Accessed June 25, 2020. https://www.neocate.com/junior/