Research Paper

Calcitriol treatment in metabolic bone disease of prematurity with elevated parathyroid hormone: A preliminary study

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ABSTRACT

Objective: To describe the association of calcitriol treatment with the change in parathyroid hormone (PTH) and biochemical markers of bone disease in infants with metabolic bone disease of prematurity (MBD) and secondary hyperparathyroidism.

Study design: This retrospective chart review examined serum intact PTH, serum calcium (Ca), serum phosphorus (P), serum alkaline phosphatase (APA), urine calcium/creatinine (UCa/Cr), and tubular reabsorption of phosphate (TRP) in 32 infants prior to and following calcitriol treatment for MBD with PTH >100 pg/ml. 25-hydroxyvitamin D concentrations were recorded.

Results: Following calcitriol treatment, PTH decreased from median (min/max) 220 (115/593) to 25 (3/259) pg/ml, $p < 0.001$; Ca increased from 9.9 (8.9/10.7) to 10.3 (9.7/11.3) mg/dl, $p < 0.001$; P increased from 4.3 (2.7/6.4) to 5.4 (2.9/7.4) mg/dl, $p = 0.001$; and TRP increased from 81 (59/98) to 91.5 (78/98) %, $p = 0.03$. APA did not differ pre-treatment: 616 (209/1193) vs. post-treatment 485 (196/1229) U/L, $p = 0.12$. Vitamin D deficiency was not present. Hypercalcemia with hypercalciuria occurred in 3/32 subjects, all normalized after dose reduction.

Conclusion: Improvements in MBD markers and lack of serious adverse effects suggest calcitriol may be a treatment option in infants with MBD and secondary hyperparathyroidism.

Metabolic bone disease of prematurity (MBD), a term often used interchangeably with osteopenia or biochemical rickets of prematurity, is defined as decreased bone mineral content relative to the expected content for an infant of comparable size or gestational age in conjunction with biochemical or radiographic changes. MBD remains a significant health care concern amongst pre-term and small for gestational age infants, as current reports indicate that 10–20% of extremely low birth weight (ELBW, birth weight <1000 g) premature infants have radiographic evidence of rickets [1]. This rate likely underestimates the true incidence of MBD of prematurity as significant loss of bone mineralization is needed before characteristic radiographic changes are visible [2].

Strategies for preventing and treating MBD include fortification of breast milk and use of preterm formulas [3–5]. The recommended intake of calcium and phosphorus is 150–220 mg/kg/day and 75–140 mg/kg/day, respectively [3]. Unfortunately, in a subpopulation of neonates, introduction of fortified feeds is delayed or contraindicated [e.g. those with necrotizing enterocolitis (NEC), bowel resection, feeding intolerance] and these infants cannot benefit from increased calcium and phosphorus present in fortification. Additionally, while total parenteral nutrition (TPN) may allow for achievement of normal biochemical status, it frequently cannot provide sufficient mineral replacement to match *in utero* rates of mineral accretion.

Phosphorus deficiency from inadequate intake is the typical mechanism underlying much MBD, and biochemical profiles often demonstrate decreased serum phosphorus (P), elevated serum

alkaline phosphatase (APA), normal serum intact parathyroid hormone (PTH), normal or even increased serum calcium (Ca) through increased 1,25 hydroxyvitamin D [1,25(OH)$_2$D, calcitriol] production, and enhanced renal tubular reabsorption of phosphate (TRP). However, in other infants, calcium deficiency is the overriding abnormality. This inadequate calcium intake prompts excess PTH secretion and urinary phosphate wasting. The role of PTH in MBD of prematurity has received limited attention: a case series of three subjects [6], a large retrospective case series reporting PTH concentration before and after calcium supplementation in infants with birth weight <1000 g [7], and a recent prospective observational study comparing PTH with APA as an early serologic marker for MBD [8]. All studies suggest a role for PTH in the screening of MBD of prematurity.

Calcitriol, the active form of vitamin D, has a number of *direct* effects that make it an attractive treatment option in the setting of MBD with increased PTH including: 1) increasing intestinal calcium and phosphorus absorption, 2) increasing renal calcium reabsorption, and 3) suppressing parathyroid gland PTH secretion via transcriptional down-regulation. Calcitriol has a shorter half-life than cholecalciferol (vitamin D3), requires neither hepatic conversion to 25-hydroxyvitamin D [25(OH)D] nor its renal activation, and can be administered either enterally or intravenously. Calcitriol used for treatment of MBD has not been extensively studied. In a case report of two infants with MBD, calcitriol treatment decreased serum APA without adverse outcomes [9].

This retrospective study reports the use of calcitriol in addition to routine nutritional management in a series of premature infants with MBD and secondary hyperparathyroidism. The aim is to describe the change in PTH and other biochemical markers of MBD following initiation of calcitriol.

Case report

Patient Z was a 3½ month old preterm infant born at 26 weeks gestation with birth weight 800 g to a mother with HELLP syndrome and pre-eclampsia. Patient Z was referred to The Children's Hospital of Philadelphia (CHOP) for NEC requiring multiple bowel resections. Patient Z's course was complicated by short bowel syndrome, chronic lung disease, and TPN cholestasis. Medications included caffeine, furosemide, and cholecalciferol. Feeding history was notable for prolonged TPN requirement with only intermittent periods of full enteral feeds. The Bone Health team, a multidisciplinary team consisting of endocrinology, pharmacy, and nutrition, was consulted after a right humerus fracture was discovered. At the initial evaluation (day of life, DOL 110), Patient Z was receiving TPN with 40 mg/kg/day elemental calcium, 63 mg/kg/day phosphorus, and 520 IU/day cholecalciferol. Initial laboratory evaluation revealed normal albumin-corrected Ca = 9.5 mg/dL (2.4 mmol/L), decreased P = 2.7 mg/dL (0.87 mmol/L), elevated APA = 1190 U/L, elevated PTH 320 pg/ml, normal 25(OH)D = 45 mg/dL (112 mmol/L), decreased TRP = 76%, and normal UCa:Cr = 0.05 mg/mg. Calcitriol 0.1 mcg/kg/day was initiated on DOL 115. Enteral feeds were started approximately 10 days later and slowly advanced with full unfortified feeds being achieved by DOL 210 with fortification by DOL 217. Calcitriol dose was decreased as feeds and mineral supplementation advanced and furosemide was discontinued (Fig. 1). During the course of treatment, intact PTH and APA concentrations decreased, while serum calcium, phosphorus, and urinary TRP increased. Hypercalcemia (Ca = 11.1 mg/dl) occurred without hypercalciuria, and resolved with dose reduction (0.025 mcg/kg/day). Patient Z was discharged home at 7 months of life (4 months after calcitriol was started) and continued on low dose calcitriol for another year.

Methods

This study was conducted through the Division of Endocrinology at The Children's Hospital of Philadelphia. The institutional review board approved the study.

Study design

For this retrospective chart review, pharmacy records were queried to identify infants prescribed calcitriol in the Neonatal Intensive Care Unit (NICU) between July 1, 2009 and May 1, 2013.

Subjects

Infants were included for gestational age less than 37 weeks, radiographic evidence of bone demineralization (as reported by radiology, typically incidental finding on films obtained for other purposes), PTH concentration >100 pg/ml, and calcitriol treatment between 1 and 12 months after birth. Exclusion criteria included
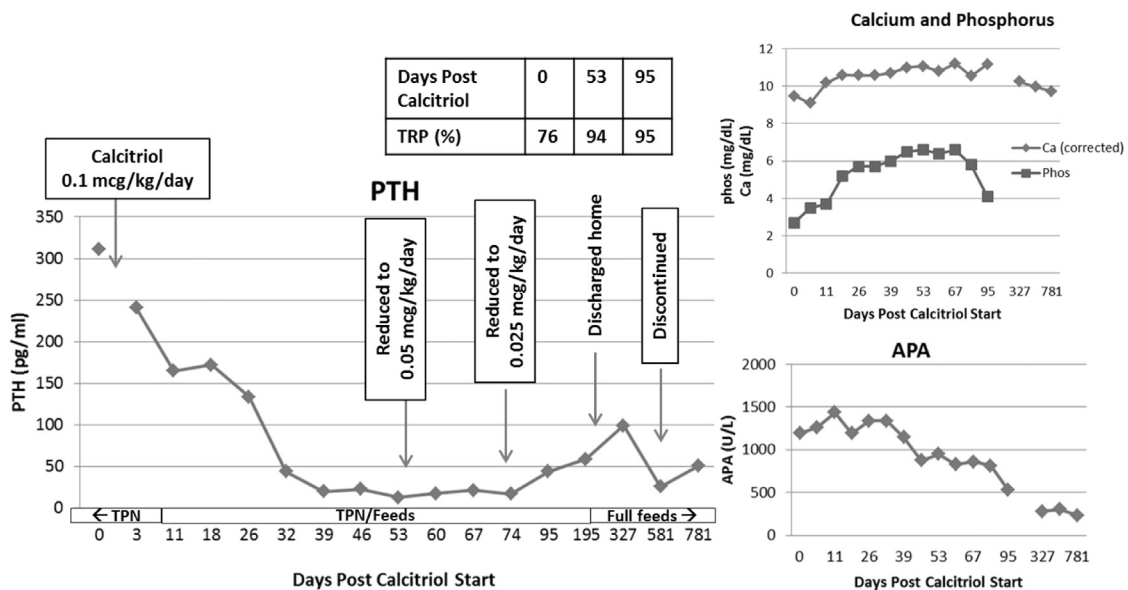

Figure 1. Patient Z's biochemical markers of bone disease during treatment with calcitriol.

Table 1
Subject characteristics ($N = 32$)

	Median (min, max)
Gestational age (weeks)	25 (23, 33)
Birth weight (grams)	692 (380, 1191)
Age at calcitriol start (days)	97 (47, 147)
Calcium intake (mg/kg/day)	40 (20, 243)
Phosphorus intake (mg/kg/day)	70 (19, 135)
Vitamin D dose (IU/day)	273 (6, 866)
	n (%)
Males	23 (73)
Fractures	17 (53)
TPN use	23 (73)
Use of bone adverse medications	29 (90)
TPN cholestasis	8 (25)
Liver failure	1 (3)
NEC (medical or surgical)	10 (31)
Other bowel surgery	9 (28)
Vitamin D deficient (<20 mg/dL)	0 (0)
Vitamin D sufficient (>30 mg/dL)	25 (78)
Calcium intake below 150 mg/kg/day[a]	27 (84)
Phos intake below 75 mg/kg/day[a]	20 (62)
Vitamin D intake below 200 IU/day[a]	4 (12.5)

[a] Calcium, phosphorus, and Vitamin D intake at time of calcitriol initiation.

significant renal insufficiency, suspected vitamin D metabolism defect, congenital parathyroid hormone defect, and lack of PTH monitoring after calcitriol initiation.

The Children's Hospital of Philadelphia (CHOP) management of MBD of prematurity

The standard of care of MBD includes maximizing mineral intake with early feeds, fortification, and direct mineral supplementation. In those neonates 1) unable to receive such standard care due to intolerance or other restrictions and 2) who have PTH >100 pg/ml, calcitriol has been used as adjunct treatment. This concentration of PTH was chosen as this value is approximately twice the upper limit for pediatric ranges (Immunolite 2000 assay).

Data collection

Data collected included basic demographics (date of birth, gestational age, birth weight, sex), coexisting medical problems, medications, intact PTH, serum Ca, serum albumin, serum P, serum creatinine (Cr), serum magnesium (Mg), APA, urine Ca, urine P, urine Cr, 25(OH)D, 1,25(OH)$_2$D, feeding/nutrition regimen, calcium intake (mg/kg/day), phosphorus intake (mg/kg/day), vitamin D intake (IU/day), calcitriol dose (mcg/kg/day) route of administration, and corresponding dates. Biochemistry (Ca, P, APA, Mg, Cr, urine P, urine Cr, urine Ca) results were recorded for the 14 days prior to baseline PTH as well as the 7 preceding days and 7 days following any subsequent PTH measurement.

Radiographic description of bone disease as reported by the radiologist was also recorded:

- Grade 1 – Loss of dense white lines at metaphyses, increased submetaphyseal lucency, and/or thinning of cortex
- Grade 2 – Any changes of Grade 1 plus irregularity and fraying of the metaphyses, or with splaying or cupping
- Grade 3 – Any changes of Grade 1 with evidence of fractures

Assays and analyses

Serum intact PTH values were measured using the immunoassay system IMMUNOLITE 2000 (Siemens Healthcare Diagnostics, Deerfield,

IL). Reference ranges for intact PTH are pediatric specific reference range (9 – 56 pg/ml). Serum Ca, P, APA, Mg, albumin, and urine electrolytes were measured with a Microslide chemistry system using Vitros 5600 and Vitros 5,1 (Ortho Clinical Diagnostics, Raritan, NJ).

Data analyses

Biochemistry results obtained simultaneously with PTH were used. For cases in which biochemistry was not obtained simultaneously with the baseline PTH, the average of two weeks of biochemistry data obtained prior to calcitriol initiation was used. For subsequent PTH values for which concomitant biochemistry were not available, the first set of biochemistry data that were obtained within the ensuing 7 days were used.

Values above or below the limit of detection were substituted with the value at the level of detection (e.g. PTH <3 pg/ml became 2.9 pg/ml and APA >1500 U/L became 1501 U/L). Calcium is reported as albumin-corrected calcium using the formula: $0.8 \times (4 g/dl - albumin) + Serum Ca$. Vitamin D deficiency was defined as 25(OH)D < 20 mg/dl.

Day of life and days after calcitriol initiation were calculated. Because frequency of laboratory evaluations varied among patients, the time frame following calcitriol initiation was expressed in two-week intervals.

Continuous data were presented as median (minimum/maximum); categorical data were presented as proportions. Non-normally distributed continuous data were analyzed using Wilcoxon Sign Rank Test. Statistical analyses were performed with Stata version 13 (Stata Corp, College Station, TX) and p-value <0.05 was used to indicate significance.

**Results**

Subject characteristics

Thirty-two neonates met inclusion and exclusion criteria (Table 1). Two neonates were excluded for renal failure, and one was excluded for PTH not measured after calcitriol initiation. Calcitriol was started no earlier than 6 weeks after birth. Many subjects (53%) had at least one fracture identified during the hospitalization. Most were on bone adverse medications (i.e. loop diuretics, caffeine, glucocorticoids). Vitamin D deficiency was not present. Most subjects were receiving TPN (73%) when calcitriol was initiated. Most subjects were below the recommended intake of calcium (<150 mg/kg/day) and phosphorus (<75 mg/kg/day). Those on TPN were receiving less calcium compared to those on fortified feeds (Table 2).

Calcitriol starting dose, median (min/max), was 0.05 (0.03/0.1) mcg/kg/day. Median dose throughout treatment was 0.08 (0.02/0.2) mcg/kg/day. Treatment was continued for a median of 207 (17/581) days. Thirteen (40%) subjects were started on enteral calcitriol and nineteen (60%) were started on intravenous calcitriol.

Table 2
Calcium, phosphorus, and Vitamin D intake at onset of calcitriol[a]

Diet regimen	Calcium (mg/kg/day)	Phosphorus (mg/kg/day)	Vitamin D (IU/day)
TPN exclusive ($n = 17$)	40 (20, 60)	68 (21, 94)	260 (120,400)
TPN + feed ($n = 6$)	45 (37, 155)	75 (19, 95)	316 (6,481)
Unfortified feeds ($n = 3$)	40 (40, 138)	21 (20, 47)	410 (73,419)
Fortified feeds ($n = 6$)	168 (114,243)	88 (61, 135)	597 (193, 866)
All combined ($n = 32$)	40 (20, 243)	70 (19, 135)	273 (6, 866)

[a] Results reported as median (min, max).

Figure 2. PTH trend on calcitriol for 32 subjects[a,b].
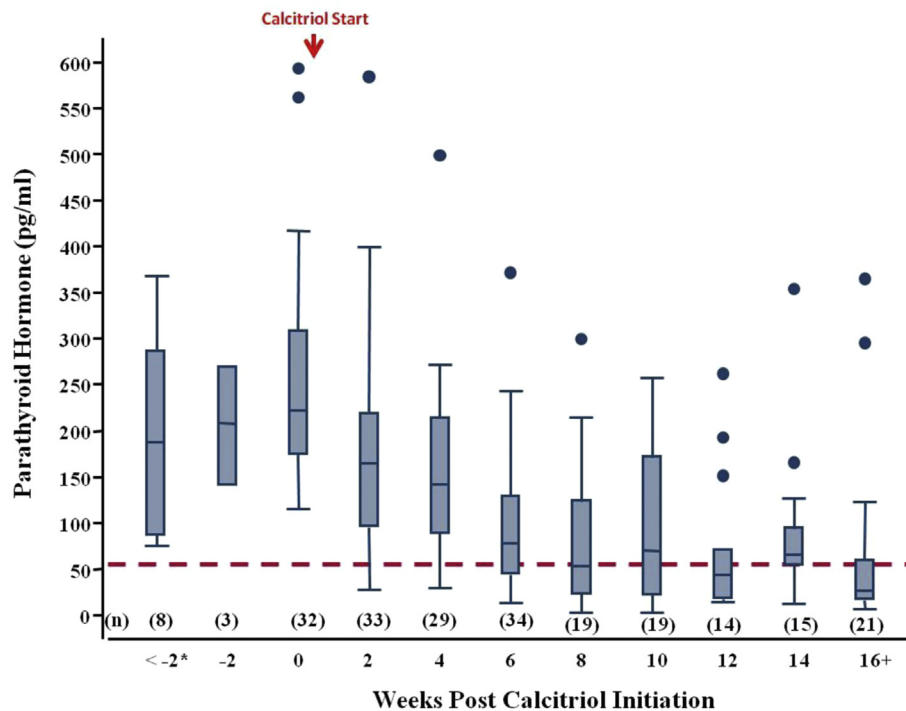
a Dashed line represents PTH = 55 pg/ml, the upper limit of normal.
b (n) number of observations

Biochemical changes post-calcitriol

PTH prior to calcitriol initiation remained steadily elevated (Fig. 2). Following calcitriol treatment, PTH decreased (Table 3). PTH reached its nadir on average by 61 (4/487) days. PTH normalized (PTH <55 pg/ml) on average by 38 (8/487) days.

Serum Ca (albumin-corrected), serum P, and TRP increased after calcitriol treatment (Table 3, Fig. 3). Serum APA and UCa:Cr did not differ compared to pretreatment values.

Nutritional intake

Calcium intake increased after calcitriol initiation, whereas phosphorus intake remained stable around 75 mg/kg/day (Fig. 4). Prior to initiation of feeds, the phosphorus content exceeded calcium content when given via the parenteral route (Table 2).

Biochemistry based on radiographic grade

Compared to Grade 1 radiographic findings, those with Grade 3 had higher APA, but no significant difference in Ca, P, or PTH (Table 4).
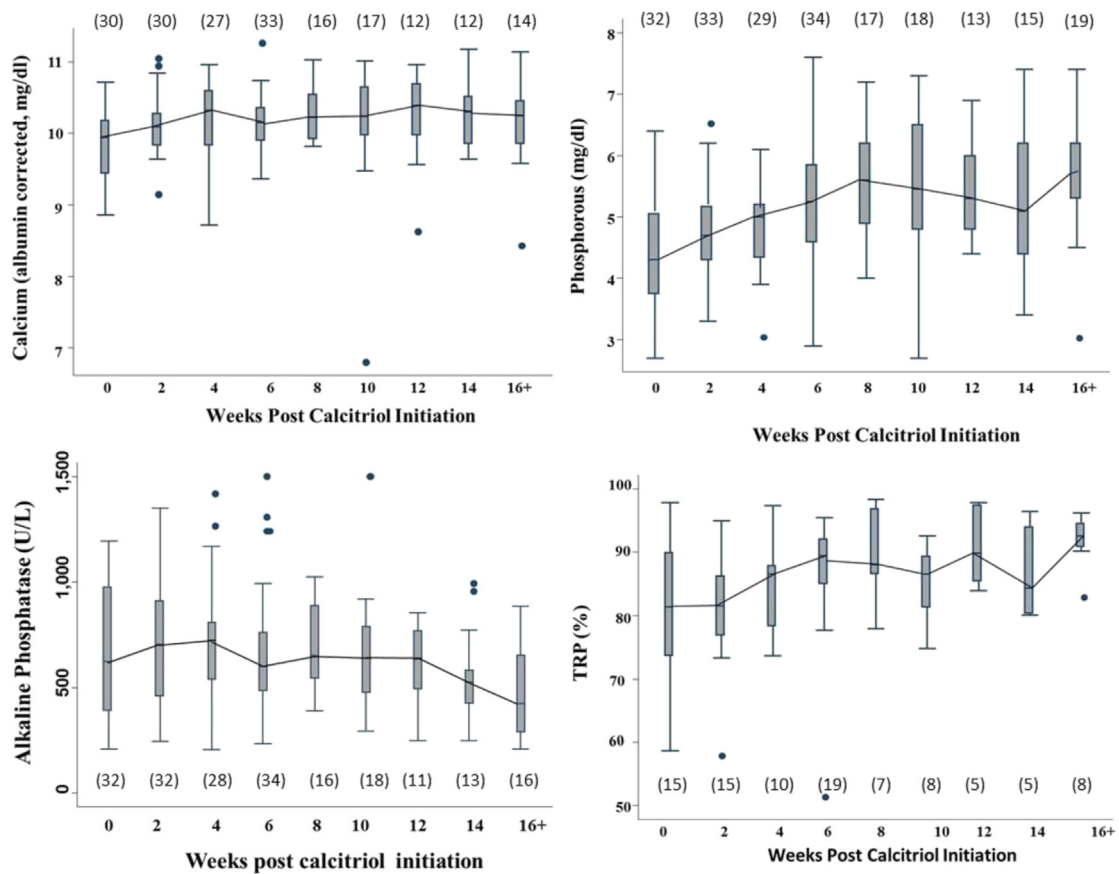
Complications

PTH suppression (<10 pg/ml) was found in 8/32 subjects, but calcitriol had already been discontinued in three of those subjects when PTH suppression occurred. In the five subjects with PTH <10 pg/ml while on calcitriol treatment, PTH suppression occurred 122 (54/228) days post treatment initiation. Hypercalciuria (UCa/Cr > 1 mg/mg) was found in 9/32 subjects. In those neonates with hypercalciuria, five were on loop diuretics and/or caffeine at the time of hypercalciuria. Hypercalcemia (Ca >11 mg/dl) was

Table 3
PTH and biochemistry change from baseline to PTH nadir

	Baseline	At PTH nadir	Difference	p-value
PTH (pg/ml)	220 (115, 593)	25 (3, 259)	−181 (−69, −584)	<0.001
	n = 32	n = 32	n = 32	
Ca (mg/dl)	9.9 (8.9, 10.7)	10.3 (9.7, 11.3)	+0.56 (−0.66, 1.55)	<0.001
	n = 30	n = 26	n = 26	
Phos (mg/dl)	4.3 (2.7, 6.4)	5.4 (2.9, 7.4)	+1.1 (−1.5, 3.85)	0.001
	n = 32	n = 29	n = 29	
APA (U/L)	616 (209, 1193)	485 (196, 1229)	−112 (−920,680)	0.12
	n = 32	n = 27	n = 27	
TRP (%)	81 (59, 98)	91.5 (78, 98)	+7.7 (−9.7, 33)	0.03
	n = 15	n = 10	n = 10	
Ur Ca/Cr (mg/mg)	0.31 (0.01, 0.95)	0.14 (0.04, 1.7)	−0.06 (−0.52, 1.6)	0.87
	n = 21	n = 19	n = 14	

Data shown is median and (min, max).

ᵃ (N) number of observations

Figure 3. APA, TRP, Calcium, and Phosphorus trend (N)ᵃ.

found in 6/32 subjects; in 3 of these 6 subjects, hypercalcemia co-occurred with hypercalciuria. However, in general, their PTH was not suppressed: 15.6 pg/mL (6.1/26). The combination of hyper-calciuria and hypercalcemia normalized after dose reduction. No nephrocalcinosis was reported, but ultrasound was not performed routinely.

Discussion

In this retrospective study, calcitriol treatment was associated with PTH reduction in premature infants with MBD and secondary hyperparathyroidism. This decline was associated with improve-ments in urinary phosphate wasting and serum phosphorus, but decrease in alkaline phosphatase was not consistent. Our findings suggest that in a subset of neonates with MBD in whom calcium deficiency is the major issue and in whom limited means to replace calcium are available, pharmacologic treatment with calcitriol is a potential option.

While calcitriol is the active form of vitamin D, its use was not based on vitamin D deficiency as none of the subjects were defi-cient. Absence of hypovitaminosis D in our cohort is consistent with other reports of normal 25(OH)D concentrations in the majority of cases of MBD, and the finding of similar 25(OH)D concentrations in preterm infants with and without rickets [10]. Instead, calcitriol was chosen because at pharmacologic doses it appears to directly suppress PTH secretion, thereby decreasing PTH-mediated urinary phosphorus wasting and bone resorption. Calcitriol may provide some benefit in increasing intestinal calcium and phosphorus ab-sorption. Importantly, preterm infants can require very small

calcitriol doses which may only measure out to 0.05–0.1 mL (1–2 drops of drug according to United States Pharmacopeia measure-ments). Due to the significant binding of calcitriol to plastic [11], a large percentage of a dose could be lost to adsorption. Diluting enteral doses being administered via feeding tubes with additional water and flushing with twice the volume of the tube to ensure the total dose is administered may be reasonable. Moreover, calcitriol can be given intravenously; intravenous and enteral doses are equivalent.

In a similar retrospective study, Moreira et al. found elevated PTH (>88 pg/ml) in 85% of preterm ELBW infants with evidence of bone demineralization on x-ray (*n* = 66). These subjects were treated with oral calcium carbonate 100 mg/kg/day, and a reduction in PTH was found after 6 weeks [7]. Certainly opti-mizing calcium intake is ideal, but oral calcium supplementa-tion is not a viable or effective treatment option for many patients with severe bowel disease/malabsorption. Moreover, delivery of additional calcium and phosphorus is often not possible with TPN alone due to limits with precipitation and stability of TPN formulation. Underscoring the feeding limita-tions and the high rate of TPN dependence in our study popu-lation, calcium intake was below the limits of recommended intake. Importantly, in our cohort, prescribed parenteral phos-phorus often exceeded the prescribed calcium; presumably this imbalance arose to manage low serum phosphorus concentra-tions. The extent to which this enhanced phosphorus delivery directly stimulated PTH secretion [12] in the presence of hypophosphatemia is not known but may need to be considered in such clinical situations.
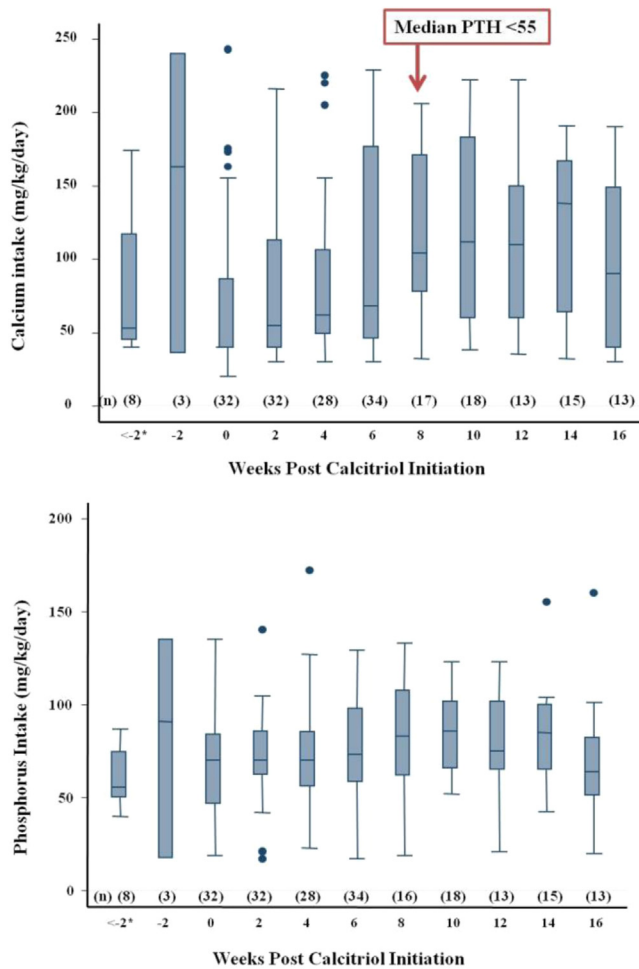
[a] <-2 weeks encompasses all data more than 2 weeks prior to calcitriol start (62 days prior is earliest observation)
[b] (n) number of observations

Figure 4. Calcium and Phosphorus intake[a,b].

Given the retrospective nature of this study, improvements in bone mineral outcomes cannot be strictly attributed to calcitriol therapy. Improved calcium delivery that occurred either concomitantly with or following calcitriol initiation may have contributed to these findings. However, prior to calcitriol, PTH remained persistently elevated and declined by the first 2 week interval after

Table 4
Biochemistry by bone class

Bone class	Class 1 (n = 14)	Class 2 (n = 1)	Class 3 (n = 17)	p-value (class 1 vs 3)
PTH (pg/ml)				
Median	245	167	203	0.5
Min, max	(115, 561)		(143, 593)	
Ca[a] (mg/dl)				
Median	10.1	10.2	9.6	0.22
Min, max	(8.9, 10.7)		(9, 10.5)	
Phos (mg/dl)				
Median	4.3	4.8	4.3	0.34
Min, max	(3.3, 6.4)		(2.7, 5.9)	
APA (U/L)				
Median	489	212	791	0.04
Min, max	(209, 1042)		(279, 1193)	

[a] Albumin-corrected calcium.

calcitriol initiation. This decline occurred without substantial change in calcium intake.

This study also presents support for the use of TRP and PTH as screening tools for MBD. TRP is elevated in nutritional phosphate deficiency, but low in the setting of renal tubular damage as well as hyperparathyroidism. Thus, if TRP is low, PTH can be used to distinguish hyperparathyroidism from primary renal phosphate wasting arising from tubular injury. The confines of using APA to diagnose or guide management of MBD are well recognized. In this cohort, APA was >350 U/L in over 80% and >500 U/L in over 60%. In general, APA decreased over time except in nine subjects in whom APA was <500 U/L at baseline. In the remaining four, APA essentially remained unchanged or increased slightly (data not shown); the extent to which this lack of improvement reflects underlying cholestasis cannot be assessed from this study. While APA >1000 U/L is sensitive for diagnosing MBD [1], our median APA was much lower for all classes of MBD radiographic description. In this study, MBD was largely defined by presence of radiological changes, but the explanation for the lower than expected APA levels in a subset of subjects with MBD cannot be determined by this study. This relationship between APA and PTH could be examined in future studies of MBD.

This retrospective study has several additional limitations. In the absence of a control group, the extent to which PTH would have

improved in the absence of calcitriol cannot be estimated. In the 8 subjects for whom PTH was monitored before treatment, the PTH did not generally decrease prior to calcitriol. Additionally, PTH >100 pg/ml was arbitrarily set as representing a hyperparathyroid state. Moreira et al. used PTH>88 pg/ml to define hyperparathyroidism when initiating treatment with calcium, but found in a later study that PTH >180 pg/ml at 3 weeks of life was useful in detecting severe MBD [7,8]. The exact threshold for PTH has yet to be defined in neonates and is worthy of further study. 1,25(OH)$_2$D levels were not routinely measured and, thus, the relationship between PTH and 1,25(OH)$_2$D, if any, in our subjects with MBD cannot be evaluated. In vitamin D deficiency, 1,25(OH)$_2$D levels can be low, normal, or elevated, and in preterm infants, reference data are not available. Future studies examining the contribution of 1,25(OH)$_2$D concentration will likely provide insight into the pathophysiology of MBD at least in a subset of patients. Timing of labs was not consistent among patients, and data were not always available simultaneous with the PTH concentration. Nutritional data were examined on a day that corresponded with labs, but may not reflect the intake from the preceding weeks.

Complications may be underestimated as biochemistry labs, particularly urine studies, and renal ultrasounds were not routinely obtained. The extent to which calcitriol impacts clinically relevant outcomes (incidence of fractures, DXA scores, quality of life scores) beyond laboratory markers of MBD is not clear. Radiographic films were not followed over time, and no protocol for radiographic follow-up in MBD currently exists. Finally, the prevalence of fractures, GI disturbances, and other health issues in this cohort from a quaternary care NICU with a large surgical referral base was quite high. These comorbidities distinguish this neonatal population from the more typical preterm infants who do not face such challenges. Thus, while this study was conducted in a relatively critically ill population, it provides a potential treatment option for this "less typical" NICU population in whom MBD in the setting of secondary hyperparathyroidism may be more problematic.

Conclusion

Overall improvements in MBD markers suggest calcitriol may be a viable option in patients with severe bone disease complicated by secondary hyperparathyroidism, in particular when other treatment options are not available. This study highlights the need for clinical trials to compare markers of bone disease, clinical outcome, and adverse effects in those managed with routine treatment alone versus those in whom calcitriol is used as an adjunct.

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