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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

*Abbreviations:* PTH, Parathyroid Hormone; MBD, Metabolic Bone Disease; Ca, Calcium; P, Phosphorus; APA, Alkaline Phosphatase; UCa/Cr, Urinary Calcium:-Creatinine; TRP, Tubular Reabsorption of Phosphate; ELBW, Extremely Low Birth weight; NEC, Necrotizing Enterocolitis; TPN, Total Parenteral Nutrition; $1,25(OH)_2D$, 1,25 hydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; NICU, Neonatal Intensive Care Unit; DOL, Day of Life; CHOP, The Children's Hospital of Philadelphia.

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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

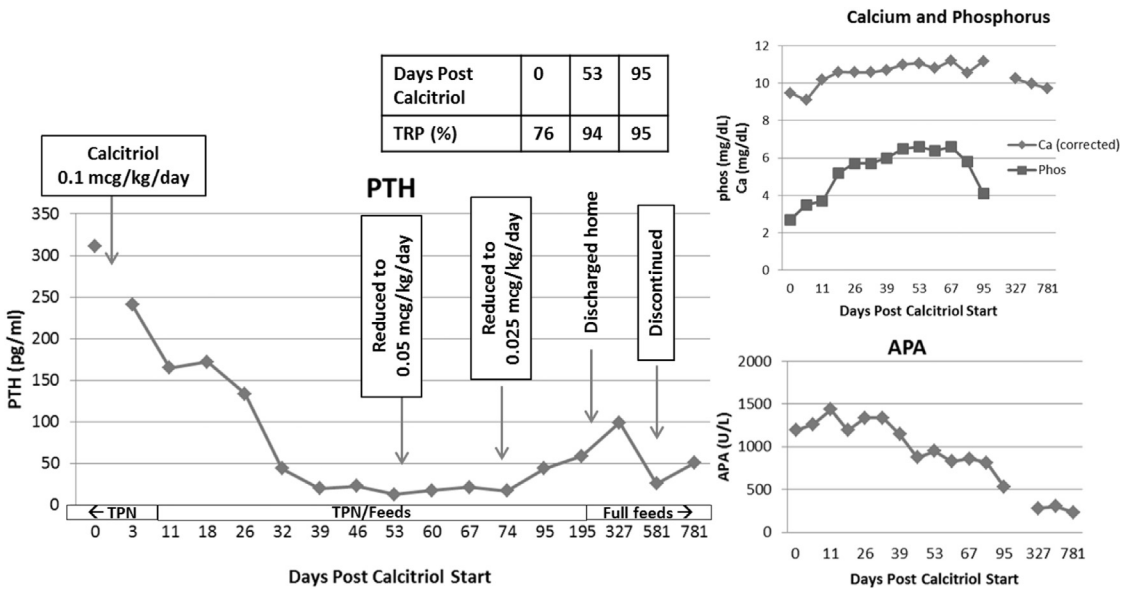


**Figure 1.** Patient Z's biochemical markers of bone disease during treatment with calcitriol.