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Case Report

# Fractures and Osteomalacia in a Patient Treated With Frequent Home Hemodialysis

Mark R. Hanudel, MD, MS,[1] Larry Froch, MD,[2] Barbara Gales, RN,[1] Harald Jüppner, MD,[3,4] and Isidro B. Salusky, MD[1]

Bone deformities and fractures are common consequences of renal osteodystrophy in the dialysis population. Persistent hypophosphatemia may be observed with more frequent home hemodialysis regimens, but the specific effects on the skeleton are unknown. We present a patient with end-stage renal disease treated with frequent home hemodialysis who developed severe bone pain and multiple fractures, including a hip fracture and a tibia-fibula fracture complicated by nonunion, rendering her nonambulatory and wheelchair bound for more than a year. A bone biopsy revealed severe osteomalacia, likely secondary to chronic hypophosphatemia and hypocalcemia. Treatment changes included the addition of phosphate to the dialysate, a higher dialysate calcium concentration, and increased calcitriol dose. Several months later, the patient no longer required a wheelchair and was able to ambulate without pain. Repeat bone biopsy revealed marked improvements in bone mineralization and turnover parameters. Also, with increased dialysate phosphate and calcium concentrations, as well as increased calcitriol, circulating fibroblast growth factor 23 levels increased.
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Although hyperphosphatemia is common in end-stage renal disease (ESRD), hypophosphatemia may also occur. Patients with ESRD treated with frequent home hemodialysis often have such high rates of phosphate removal so as to require the addition of phosphate to the dialysate solution in order to prevent hypophosphatemia.[1] However, the long-term skeletal consequences are unknown. In individuals with normal kidney function, chronic hypophosphatemia may lead to impaired bone mineralization and osteomalacia, which may present clinically as bone pain and/or fractures. We present a case of symptomatic osteomalacia in a patient on frequent home hemodialysis therapy, treated with the addition of phosphate to the dialysate solution, calcium supplementation, and active vitamin D sterols. Furthermore, we demonstrate the response of circulating fibroblast growth factor 23 (FGF-23) levels to such therapy changes.

## CASE REPORT

A 52-year-old white woman with ESRD presented to the orthopedic clinic for a poorly healing tibia-fibula fracture. She sustained the left leg fracture with minimal trauma 8 months prior to presentation, and the fracture had yet to heal, requiring a short leg cast that was serially changed. She had an extensive fracture history, including a fractured hip 12 months prior to presentation, a pubic ramus stress fracture, and metatarsal and metacarpal fractures. She also reported right tibia pain. Her bone pain and multiple fractures rendered her nonambulatory and wheelchair bound for 17 months prior to presentation. She was referred to our Bone Clinic, where x-rays revealed a nonunion fracture of the left tibia and fibula, with significant osteopenia.

The patient developed ESRD secondary to suspected Alport syndrome at 14 years of age and started dialysis. She underwent 3 failed kidney transplantations, the last of which occurred 12 years prior to presentation, and had been dialysis dependent for a total of 30 years. Her medical history also included subtotal parathyroidectomy 35 years prior to presentation and sensorineural hearing loss. The patient was receiving home hemodialysis via a left upper-extremity arteriovenous fistula, 4 sessions per week, 7 hours per session, using a Fresenius 2008K home machine, with a blood flow rate of 220 mL/min, dialysate flow rate of 300 mL/min, and dialysate composition of 2 mEq/L of potassium, 2.5 mEq/L of calcium, and 35 mEq/L of bicarbonate. She was anuric. The patient took ergocalciferol, 50,000 IU, weekly and calcitriol, 0.25 μg, daily. She was not treated with calcium supplements or phosphate binders. Her diet included dairy products, and daily dietary phosphate intake was ~600 mg.

Review of the patient's laboratory results revealed chronic hypophosphatemia, with serum phosphate levels ranging from 1.9 to 2.9 mg/dL for several months prior to the clinic visit, and a nadir value of 1.5 mg/dL during the year prior to presentation.

*From the Departments of [1]Pediatrics and [2]Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA; and [3]Endocrine Unit and [4]Division of Pediatric Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.*

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*Address correspondence to Mark R. Hanudel, MD, MS, UCLA Department of Pediatrics, Division of Pediatric Nephrology, 10833 Le Conte Ave, MDCC A2-383, Los Angeles, CA 90095-1752. E-mail: mhanudel@mednet.ucla.edu*



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Serum calcium levels were low-normal in the months prior to the clinic visit (8.5-9.0 mg/dL), and several ionized calcium measurements during this period were <1.10 mmol/L. In the setting of this mild hypocalcemia, intact parathyroid hormone levels ranged from 24 to 53 pg/mL; more remote levels were in the high-30- to low-40-pg/mL range. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were sufficient at 76 ng/mL and 52 pg/mL, respectively. Plasma carboxy-terminal (total) FGF-23 level was 152 RU/mL, and intact (bioactive) FGF-23 level was 55 pg/mL, low values for a dialysis patient, likely reflecting the consequences of hypophosphatemia.

Given the history of fractures, bone pain, and persistent hypophosphatemia, a bone biopsy after double tetracycline labeling was performed, which revealed markedly increased osteoid volume, surface, and thickness; zero percentage mineralizing surface; a mineral apposition rate of zero; an infinite mineralization lag time; and a bone formation rate of zero (Table 1). These findings were consistent with a severe mineralization defect, and osteomalacia was diagnosed.

Given the diagnosis of osteomalacia in the setting of hypophosphatemia and hypocalcemia, several changes were made to the patient's treatment regimen. First, phosphate was added to the dialysate solution. With every hemodialysis treatment, 1 Fleet enema solution (118 mL, with a phosphate concentration of 1.38 mmol/mL; Fleet Laboratories) was instilled directly to the dialysate, resulting in a dialysate phosphate concentration of 1.3 mmol/L. Additionally, dialysate calcium concentration was increased from 2.5 to 4.0 mEq/L, and calcitriol dose was increased from 0.25 μg daily to 0.5 μg daily.

Within a few weeks, the patient's pain markedly diminished. Serum phosphate and calcium levels increased (although there were temporary decreases, most values were higher), and alkaline phosphatase levels steadily decreased, suggestive of improving bone mineralization (Fig 1). Over time, carboxy-terminal FGF-23 levels increased 57%, and intact FGF-23 levels increased 222%. Six months after the clinic visit, there was some radiographic evidence of fracture healing, so the patient was transitioned from a cast to a lower-leg walking boot. Repeat bone biopsy, performed 18 months later, revealed marked improvements in mineralization parameters, including normalized mineral apposition rate, improved percentage mineralizing surface, improved mineralization lag time, and improved bone formation rate (Table 1). By then, the patient was pain free, no longer required the lower-leg boot, and was walking without difficulty.

**Table 1.** Bone Histomorphometry Before and After Addition of Phosphate to the Dialysate

| Histologic Variable | Before Treatment | After Treatment | Reference Range[a] |
|---|---|---|---|
| Bone volume/tissue volume, % | 29.0 | 38.3 | 21.8 ± 7.2 |
| Osteoid volume/bone volume, % | 35.4 | 47.9 | 1.6 ± 1.9 |
| Osteoid surface/bone surface, % | 83.4 | 76.5 | 9.2 ± 8.4 |
| Osteoid thickness, μm | 27.3 | 29.2 | 10.8 ± 3.2 |
| Bone formation rate/bone surface, $\mu m^2/mm^2/d$ | 0 | 14.1 | 25.2 ± 10.8 |
| Mineralizing surface/bone surface, % | 0 | 3.3 | 12.0 ± 5.0 |
| Mineral apposition rate, μm/d | 0 | 1.1 | 0.7 ± 0.1 |
| Adjusted apposition rate, μm/d | 0 | 0.1 | 0.5 ± 0.2 |
| Mineralization lag time, d | ∞ | 577.5 | 23.7 ± 2.7 |

[a]Mean ± standard deviation for adult women.[21,22,23]

## DISCUSSION

This case demonstrates the consequences of long-term hypophosphatemia and hypocalcemia in a patient treated with frequent home hemodialysis. Bone fragility is common in dialysis patients and may precipitate fractures. In dialysis populations, fracture prevalence ranges from 10% to 40%, with even higher percentages observed in patients older than 50 years.[2] Hip fractures[3,4] and long bone fractures[5] in dialysis patients are associated with increased mortality. Children with chronic kidney disease, in whom mineralization defects are common,[6] are also at risk for fractures.[7]

Renal osteodystrophy is defined as alterations in bone morphology associated with chronic kidney disease; it is quantifiable by bone biopsy histomorphometry.[8] The 5 subtypes of renal osteodystrophy (mild, osteitis fibrosa, osteomalacia, adynamic, and mixed) are classified on the basis of bone turnover and mineralization.[2] Turnover is quantified by bone formation rate, and mineralization, which reflects the amount of unmineralized osteoid, is measured by mineralization lag time.[2] A large retrospective study of dialysis patients found a higher frequency of fractures in patients with osteomalacia compared with those with other types of renal osteodystrophy.[9]

Our patient developed severe osteomalacia, characterized by a major decrease in osteoid mineralization. Because bone matrix mineralization requires normal concentrations of phosphate and calcium, any process causing hypophosphatemia and/or hypocalcemia may engender suboptimal mineralization. Our patient had both chronic hypophosphatemia and relative hypocalcemia despite sufficient vitamin D levels. Although both phosphate and calcium deficiencies are potentially associated with the development of osteomalacia, we believe that prolonged and persistent hypophosphatemia played a predominant role in the pathogenesis of this patient's severe mineralization defect. Within weeks after the addition of phosphate to the dialysate, the patient's bone pain markedly diminished.

The amount of hemodialysis the patient received likely contributed to the hypophosphatemia.[10,11] A recent study of home hemodialysis patients receiving 17.5 hours of dialysis per week found that an average of 4.16 g of phosphate was removed weekly.[12] This is nearly double the average amount of phosphate removed (2.36 g) in a study of traditional thrice-weekly hemodialysis patients who received an average of 11.5 hours of dialysis per week.[13] Our patient received 28 hours of hemodialysis weekly and