

High Fibroblast Growth Factor (FGF) 23: An Unusual Cause of Severe Osteoporosis in a Patient with Chronic Liver Disease

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Case Description

A 14-year old boy with autoimmune hepatitis who was on long term oral steroids for 10 years, presented with acute onset lower back pain without preceding trauma. Lumbar spine radiograph (Figure 1) showed severe osteopenia and compression fractures of vertebrae T12 to L1. Bone mineral density Z-score at the lumbar region was -4.9. Biochemically, there was hypocalcaemia and severe hypophosphataemia with adjusted calcium 2.03 (2.20 - 2.65) mmol/L and phosphate 0.87 (1.18 - 1.89) mmol. Serum PTH levels were normal at 2.3 (1.3 - 9.3) pmol/L. Serum 25-hydroxy-vitamin-D3 was insufficient at 14.9 ug/L despite him being on daily cholecalciferol 1000 units for vitamin D deficiency from cholestasis-induced malabsorption. Urine phosphate levels were grossly elevated at 8.3 (1.29 - 1.94) mmol/L. Work up for renal tubular acidosis was negative.

The patient was started on calcium, phosphate and vitamin D replacements and treated with intravenous bisphosphonates. Despite supraphysiological doses of oral phosphate replacement at 3 mmol/kg/day, phosphate levels remained suboptimal at 0.8-0.9 mmol/L. High serum levels of fibroblast growth factor 23 (FGF23) at 840 (<230) RU/mL was detected. As the age of onset of the hypophosphataemia made hereditary hypophosphataemic rickets (HHR) an unlikely cause for this, alternatives were sought. A Ga68-DATONAC PET-CT was performed to screen for tumour-induced osteomalacia which is a known cause of high FGF23, and this returned negative. The high FGF23 was therefore attributed to the patient's underlying chronic liver disease, a previously described phenomenon.

The patient underwent a living-related liver transplant for end-stage liver disease (ESLD) 6 months later. Two months post-transplant, phosphate levels normalized and FGF23 levels dropped to 180 RU/mL (Figure 2). He was weaned off phosphate replacements and was able to maintain normal serum phosphate levels thereafter.

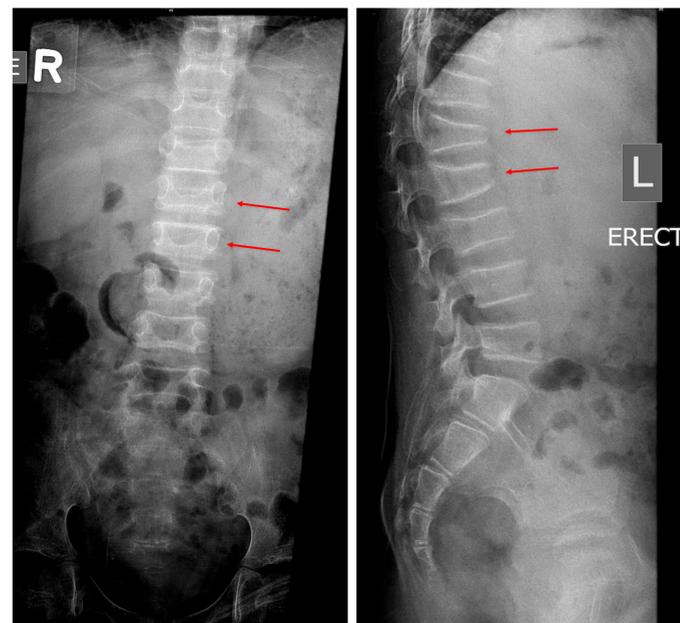


Figure 1: Supine and erect spinal radiograph of patient showing severely osteopenia bones, loss of height in the lower thoracic and lumbar vertebrae and anterior wedging in at least 2 contiguous vertebrae (T12-L1, red arrow).

FGF23 trend pre- and post-liver transplant

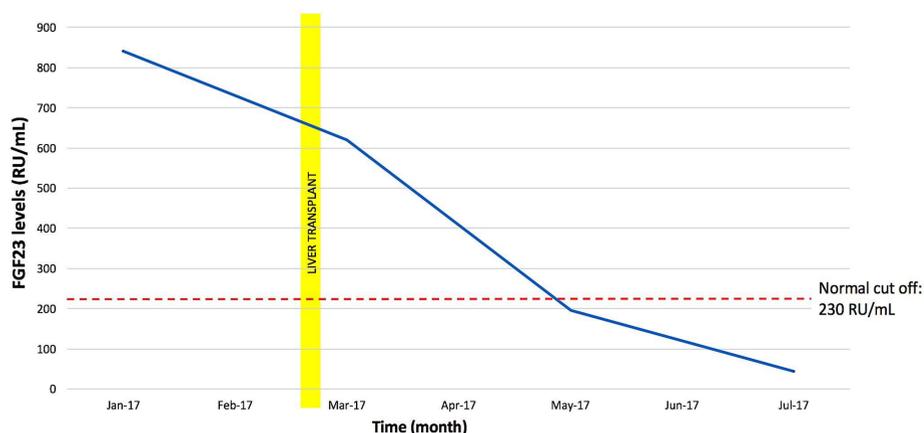


Figure 2: FGF23 trend before and after liver transplant, showing association between high FGF23 levels in ESLD, with resolution post-liver transplantation

Discussion

FGF23 is a key regulator of phosphate homeostasis and increases physiologically in response to high serum phosphate or high vitamin D concentrations. It acts at the proximal renal collecting tubules to increase urine phosphate excretion and reduces 1,25-dihydroxyvitamin-D3 production.¹ Pathologically elevated serum FGF23 is classically associated with HHR resulting from the *PHEX* gene mutation, but is also a feature of tumour-induced osteomalacia in children.^{2,3} Recently, high levels of FGF23 have also been described in patients with cholestatic liver disease and ESLD.^{4,5} In fact, elevated FGF23 mRNA expression was demonstrated in the hepatocytes of patients with ESLD. The exact mechanism triggering this overexpression in ESLD remains unknown but is postulated to be related to local inflammatory responses to hepatic injury⁵. Importantly, high FGF23 levels were shown to be independently associated with an increased risk of mortality in an adult cohort with ESLD awaiting transplant.⁵

Conclusions

High FGF23 levels may contribute to metabolic bone disease in ESLD patients and should be considered in this group of patients who develop severe osteoporosis resistant to vitamin D therapy. This condition requires treatment with high levels of phosphate and vitamin D replacements until eventual liver transplantation, which appears to provide a cure.

References

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