Elevated FGF-23 in a patient with rhabdomyolysis-induced acute kidney injury

David E. Leaf¹, Myles Wolf² and Leonard Stern³

¹Department of Medicine, Columbia University, New York, NY, ²Division of Nephrology and Hypertension, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL and ³Division of Nephrology, Department of Medicine, Columbia University, New York, NY

Correspondence and offprint requests to: Leonard Stern; E-mail: LS38@columbia.edu

Abstract
Rhabdomyolysis-induced acute kidney injury (AKI) is characterized by hyperphosphataemia and hypocalcaemia. Despite appropriate secondary elevation of parathyroid hormone (PTH) in response to hypocalcaemia, rhabdomyolysis and AKI are associated with acute deficiency of 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃), and yet, the mechanism responsible for such a deficiency remains unclear. Fibroblast growth factor 23 (FGF-23), a potent phosphaturic hormone that inhibits 25-hydroxyvitamin D₃-1α-hydroxylase, could explain the deficiency of 1,25(OH)₂D₃ in this setting. Here, we document, for the first time, elevated levels of FGF-23 in a patient with rhabdomyolysis-induced AKI.

Keywords: ARF; hyperparathyroidism; hyperphosphataemia; vitamin D

Background
Rhabdomyolysis-induced acute kidney injury (AKI) is characterized by marked elevation of muscle enzymes in association with hyperphosphataemia and hypocalcaemia. Despite appropriate secondary elevation of parathyroid hormone (PTH) in response to hypocalcaemia, skeletal resistance to the calcaemic action of PTH prevents normalization of serum calcium levels [1]. Data from a prospective study in humans [2] with rhabdomyolysis-induced AKI suggest that this skeletal resistance to PTH, in turn, may be mediated by acute deficiency of 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃), however, the mechanism responsible for such a deficiency remains unclear.

Fibroblast growth factor 23 (FGF-23) is a potent phosphaturic hormone [3,4] that inhibits 25-hydroxyvitamin D₃-1α-hydroxylase, thereby reducing renal production of 1,25(OH)₂D₃ [5]. Additionally, FGF-23 increases expression of 25-hydroxyvitamin D₃-24-hydroxylase, the enzyme responsible for the first step in the catabolism of 1,25(OH)₂D₃, thereby further reducing its activity [6].

FGF-23 levels increase progressively as chronic kidney disease (CKD) worsens, perhaps accounting for the progressive reduction of 1,25(OH)₂D₃ levels in CKD. Recently, FGF-23 has gained widespread attention for its association with increased mortality among patients with incident end-stage renal disease (ESRD) [7]. In contrast, little is known about FGF-23 levels among patients with AKI in general and rhabdomyolysis specifically. We hypothesized that FGF-23 is elevated in rhabdomyolysis-induced AKI, which could be a potential mechanism for the low levels of 1,25(OH)₂D₃ noted in previous studies of this disorder.

Case report
A 45-year-old man with a history of polysubstance abuse presented to our hospital because of chest pain, right leg pain, dark urine and decreased urine output in the setting of heavy heroin and cocaine use on the day prior to admission. His medical history included mild chronic obstructive pulmonary disease and chronic hepatitis C virus infection.

On initial evaluation in the emergency department, the patient's temperature was 98.3°F, blood pressure 94/52 mmHg, heart rate 100 beats per minute and respiratory rate 22 breaths per minute, with an oxygen saturation 100% while breathing room air. Physical examination was notable for minimal tenderness to palpation along the right anterior thigh and anterior tibia, with all compartments being soft and without edema or ecchymoses. A Foley catheter was in place draining 250 cm³ of tea-coloured urine.

Initial and subsequent laboratory studies are shown in Figure 1 and Table 1, and are notable for AKI, marked elevation of creatinine phosphokinase (CPK), hypocalcaemia and hyperphosphataemia. Urine toxicology was positive for opiates and cocaine, and a plasma alcohol level was negative. Urinalysis with microscopy revealed trace protein, 2+ blood and one red blood cell per high power field. Renal ultrasonography revealed right and left
kidneys measuring 12.0 and 12.1 cm, respectively, without evidence of hydronephrosis.

The patient was admitted to a general medicine service. He was initially oliguric, with a urine output of 100 cm³/10 hours, and was treated with bicarbonate-containing intravenous fluids as well as intravenous diuretics. His urine output subsequently increased to 450, 1640 and 2630 cm³/24 hours over the following 3 days, respectively, and diuretics were discontinued. Serum creatinine peaked on Day 7 and subsequently began to normalize. A sample of blood drawn on Day 7 was tested for FGF-23 using a second generation assay that recognizes two epitopes in the C terminus (Immutopics, San Clemente, CA) and was found to be markedly elevated (Table 1). On Day 12, the patient left the hospital against medical advice.

**Discussion**

The present study documents, for the first time, elevated levels of FGF-23 in a patient with rhabdomyolysis-induced AKI. Furthermore, to our knowledge, this is the first published report of increased FGF-23 in AKI, irrespective of aetiology.

Elevation of FGF-23 in rhabdomyolysis may explain the link between the long recognized but poorly understood paradoxical finding of 1,25(OH)₂D₃ deficiency in the setting of hypocalcaemia and hyperparathyroidism. Alternatively, it is possible that global nephron dysfunction and/or hyperphosphataemia itself may have contributed to diminished activity of 25-hydroxyvitamin D₃-1α-hydroxylase, thereby resulting in the observed deficiency of 1,25(OH)₂D₃. At least two observations in patients with CKD,
admittedly a markedly different pathophysiology than AKI, suggest that the latter mechanism may not be the case: 1,25(OH)2D3 levels begin to decline long before the development of significant nephron loss or hyperphosphataemia [8,9], and the decline in 1,25(OH)2D3 associated with increased FGF-23 is independent of glomerular filtration rate [5]. An additional finding in the current patient which supports a functional significance to the elevated levels of FGF-23 observed is the declining levels of 25(OH)D3 (Table 1). In the absence of a large increase in 1,25(OH)2D3 production, which was not seen, declining levels of 25(OH)D3 may reflect increased activity of 25-hydroxyvitamin D3-24-hydroxylase, in turn stimulated by FGF-23 [6].

The precise mechanisms responsible for elevation of FGF-23 could not be discerned in this patient. Whether due to changes in unmeasured variables, such as decreased expression of Klotho, a co-receptor for FGF-23 [10], is unknown and requires additional study. Direct stimulation of FGF-23 by hyperphosphataemia is a potential mechanism, however, no human studies have demonstrated an increase in FGF-23 levels in response to increasing serum phosphate levels, despite the fact that they are often correlated. Finally, given recent evidence that PTH stimulates FGF-23 production in the mouse model [11], FGF-23 elevation in the setting of rhabdomyolysis may simply reflect the transient secondary hyperparathyroidism that results from calcium sequestration in muscle. However, the latter mechanism has yet to be demonstrated in humans, and in fact, a recent study in uraemic CKD patients suggests that FGF-23 is actually the physiologic regulator of PTH secretion, a process that is impaired in CKD because of downregulation of Klotho and FGF receptor 1 in the parathyroid glands [12].

It remains to be determined whether elevation of FGF-23 in this setting represents an appropriate physiologic response, for example to hyperphosphataemia, or alternatively, whether its abundance is maladaptive and/or a marker of poor outcomes, as in the ESRD population [7]. Finally, it is unknown whether AKI resulting from aetiologies other than rhabdomyolysis is also associated with elevation of FGF-23. Rhabdomyolysis differs from other aetiologies of AKI in that hypocalcaemia and hyperphosphataemia are present more universally, and generally, more severely in the case of rhabdomyolysis. Whether AKI is associated with increases in FGF-23 irrespective of these electrolyte abnormalities is unknown. Future studies should address these topics, and we are currently designing such a study.

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References