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FGF23 in acute kidney injury

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Abstract

Purpose of review—to review emerging literature on changes in fibroblast growth factor 23 (FGF23) levels in the setting of acute kidney injury.

Recent findings—studies suggest that FGF23 levels are elevated in patients with acute kidney injury, and correlate with increased risk of death or need for dialysis (in adults) or prolonged ventilation time and higher fluid gain (in children). Animal work shows that the etiology behind this FGF23 increase is multi-factorial and includes increased production in bone and decreased clearance, but not vitamin D or PTH-activated pathways. Interestingly, FGF23 levels were found to be mildly elevated even in hospitalized patients without kidney injury, although this observation may be limited to only c-terminal FGF23 fragments. The prognostic implications of an elevated FGF23 value in patients with acute kidney injury need to be confirmed in larger cohorts and evaluated for long-term outcomes such as development of new CKD or CKD progression, as well as cardiovascular disease, similar to studies of FGF23 in the prevalent CKD population.

Summary—FGF23 levels are elevated in patients with AKI and are associated with morbidity and mortality is small human studies. Mechanistic work in animals suggests that the elevation is independent of PTH or vitamin D-signaling pathways. Much work remains to understand the physiology behind FGF23 elevation and the long-term effects of FGF23 in AKI.

Keywords

Mineral metabolism; phosphate; FGF23

Introduction

Fibroblast growth factor 23 (FGF23) was initially identified as the phosphaturic agent in cases of the rare genetic or acquired hypophosphatemic disorders autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia.[1, 2] Early work showed that FGF23 acts as a hormone on the kidneys to increase phosphate excretion and decrease the expression of the 25-hydroxyvitamin D activating enzyme 1-alpha-hydroxylase.[3] Interest in this phosphate-regulating hormone intensified recently, after levels were found to be

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elevated in patients with chronic kidney disease (CKD) and were later linked with increased mortality in CKD as well as incident dialysis patients.[4-7]

In this paper I will review recent publications exploring the role of FGF23 in acute kidney injury (AKI) and highlighting potential mechanisms for the elevations seen in patients and animals with AKI.

Relators of FGF23

Major regulators of FGF23 levels are calcitriol, parathyroid hormone (PTH) and dietary phosphate, although the mechanisms by which phosphate in particular affects the hormone's production are not well defined.[8] In the CKD population FGF23 levels increase with progressive loss of renal function and correlate with serum phosphate levels. Bone production has been described early on in animals and humans with CKD, although recent animal work suggests that the diseased kidney itself can make FGF23.[9-12] The effect of PTH on FGF23 is still being defined, but suggests that PTH can increase FGF23 production in bone as well as circulating levels in both animals and humans.[13, 14] The timing of elevation of FGF23 (early) and PTH (late) in CKD patients, however, suggests that, at least initially, FGF23 production is regulated by mechanisms independent of PTH.[15]

FGF23 protein is cleaved at a conserved site towards the C-terminal end of the protein. This cleavage event is presumed to be within the FGF23 producing cells and is dependent on the glycosylation state of the full-length molecule.[16] The ratio of c-terminal to intact protein in the circulation appears to be partly dependent on the iron status of the organism, with more c-terminal fragments present in iron deficiency.[17, 18] In addition, the c-terminal species of FGF23 disappear with loss of renal function such that in patients on dialysis predominantly the full-length protein can be detected.[19, 20] A pro-protein convertase, PC2, has been implicated as the FGF23 cleavage enzyme, although it is unclear if renal failure specifically affects its function or if other signaling events upstream of cleavage are affected.[21]

Effects of elevated FGF23

Elevated FGF23 levels correlate with increased urinary phosphate excretion in CKD and thus likely serve to maintain serum phosphate levels in the normal range despite loss of renal function. However, sustained supra-physiological levels of the hormone also affect cardiac myocytes, leading to hypertrophy in vitro and in animals, and suggesting a mechanism for the observed correlation of elevated FGF23 levels and cardiovascular events in the CKD population.[22-24] Similarly, FGF23 can modulate peripheral immune cell function by affecting 1-alpha hydroxylase expression in monocytes and decreasing cathelicidin synthesis.[25]

Mineral metabolism in AKI

Acute kidney injury comes with a rapid mis-regulation of minerals normally handled by the kidneys. Specifically, calcium levels frequently decrease in patients with AKI (both ionized and total calcium), and vitamin D levels also fall.[26-28] Interestingly, while both 25OH D

and 1,25OH D levels decreased in a sample of 30 patients with AKI, only the bioavailable fraction of 25OH D, calculated as the sum of the albumin-bound and free fractions, correlated with severity of sepsis and risk of death in the cohort.[29] Parathyroid hormone (PTH) is elevated, presumably as a consequence of hypocalcemia.

Serum phosphate levels can be increased in the setting of renal failure, or decreased especially in critically ill individuals or those requiring continuous renal replacement therapy. In those instances when phosphate levels are decreased, they correlate with failure to wean from breathing support, in-hospital mortality, subsequent development of CKD and long-term mortality.[30, 31] The pathophysiology of phosphate disturbances in patients with AKI is thus multifactorial and may reflect co-morbid conditions and severity of illness as much as the acute reduction in renal clearance. For instance, in a 289 ICU cohort of patients with AKI, AKI patients with sepsis or those following open heart surgery were more likely to develop hypophosphatemia prior to initiation of renal replacement than those with other illnesses.[24, 31]

Alterations in FGF23 in AKI

Elevations in FGF23 in AKI were first described in a case report presenting a patient with rhabdomyolysis.[32] Subsequently a case series reported elevated levels of FGF23 and PTH in a cohort of 12 ICU patients with AKI compared with 8 control ICU patients without AKI (median 1948 vs 252 RU/mL); samples were obtained closest to the day with peak serum creatinine.[33] FGF23 levels were higher in non-survivors compared with survivors (median 4446 vs 544), but the population overall was small. This study also was the first to show that FGF23 levels were higher than the reference range in the control ICU patients without AKI (252 RU/mL vs <180 RU/mL), despite serum phosphate, calcium and PTH levels in the normal range.

Subsequently, a larger prospective observational study of 60 hospitalized patients (30 with AKI and 30 controls) confirmed and expanded the initial observations.[34] In their paper, Leaf et al recruited patients within 48 hours of AKI (increase in serum creatinine >=0.3mg/dL or 50% from baseline) and patients matched for ward/ ICU location, age, sex and race but with stable creatinine levels <1 mg/dL. Patients were then followed prospectively and repeat mineral metabolism parameters were assessed 5 days after enrollment; composite endpoint was death or need for renal replacement therapy. FGF23 levels were significantly higher in patients with AKI compared with control patients (1471 vs 263 RU/mL) and were associated with the composite endpoint, which was met by 11 patients with AKI and none in the control group. FGF23 levels at enrollment (or within 48 hrs of AKI) were better predictors of the need for RRT than serum creatinine, or any other mineral metabolism parameters examined. Similar to the ICU study, patients without AKI also had modestly elevated FGF23 levels (median 263 RU/mL) and otherwise normal mineral metabolism parameters such as calcium, phosphate, and vitamin D metabolites.

Two other small prospective studies support these observations. Ali et al followed a cohort of 19 pediatric patients without CKD who were scheduled to undergo cardiac surgery.[35] Of those, 5 children developed AKI post-operatively. Pre-operative FGF23 levels were

higher in the patients who went on to develop AKI (median 323 vs 69 RU/mL) and peak FGF23 levels measured within 4 days post-operatively were also higher in the AKI group (median 1010 vs 196 RU/mL). Interestingly, preoperative FGF23 levels also correlated with increased fluid gain and longer ventilation time post-operatively.[35] While the authors speculate that the elevated levels pre-operatively may indicate a derangement in renal function undetectable by conventional measures such as creatinine or cystatin C, an alternative explanation would be that the pre-operative levels reflect a poorer cardiac status in those 5 patients (who as a group had a nearly double cross-clamp time during the surgery compared with controls). Elevated FGF23 levels have been reported in pediatric patients with heart failure but without CKD and correlate with severity of heart failure and left ventricular dilation.[36]

A second small population of 14 adult patients undergoing cardiac surgery, of whom four developed AKI, was followed prospectively in a similar manner by our team.[37] FGF23 levels increased in both groups post-operatively, although were higher than in the control group (15.9 fold over baseline pre-operative levels compared with 2.8 fold in patients without AKI 24 hours after surgery). Taken together, human data from these four papers consistently show elevated FGF23 levels in patients with AKI of different etiologies compared with controls.

An important point to consider is the type of FGF23 protein being detected in the circulation. The assays used in the above reports detect both the c-terminal fragment and the intact FGF23 protein. Thus it is not possible to determine if the elevated levels measured represent an increase in intact (biologically active) FGF23, c-terminal (not active) FGF23 or both. Mechanistically, the elevated circulating FGF23 levels could represent increased production of the intact protein, and/or increased cleavage of the intact protein, and/or reduced catabolism or clearance of either species. Thus it will be important to investigate the FGF23 species in patients with AKI using alternative assays.

Possible mechanisms of FGF23 elevation in AKI

A recent study in animals from our lab sheds some light on the pathophysiology of FGF23 in AKI (Table 1).[37] Specifically, we induced AKI by two different methods – folic acid and pigment nephropathy and observed elevations in both intact and c-terminal FGF23 levels as early as one hour after renal injury. In addition, we saw increased protein levels in bones of animals with AKI 24 hours after renal injury, suggesting that the elevated circulating levels are, at least partly, due to increased production in bone and possibly increased secretion (the very early rise). In this series of experiments we did not evaluate FGF23 expression in the kidneys of AKI animals as has been reported in CKD mice. Thus, it remains possible that some of the elevated circulating FGF23 levels are produced by the injured kidneys themselves. Finally, using injection of human FGF23 protein into animals with AKI we showed that clearance of FGF23 is modestly reduced in AKI, although not to the degree of rise in FGF23.[37]

In addition, using mice lacking either PTH, or the PTH receptor in osteocytes, the site of FGF23 production in chronic kidney disease, we showed that FGF23 levels increased in

experimental AKI. This suggests that PTH signaling is not necessary for the FGF23 rise in our animal model. Similarly, vitamin D receptor-deficient mice also showed elevation of FGF23 in AKI suggesting that vitamin D signaling is also not necessary for the observed FGF23 rise.[37] The role of phosphate in regulating FGF23 in the setting of AKI appears more comples. While we could make animals hypophosphatemic by diet restriction, we could not prevent the AKI-associated rise in serum phosphate and thus could not rule out its contribution to increasing FGF23 production.[37] However, as outlined above, acutely ill patients with AKI at times have low phosphate levels. Based on the small human studies above, it is likely that even these individuals will have an elevated FGF23; however, larger groups of patients need to be followed to tease out the effect of phosphate on FGF23.

The role of calcium on FGF23 production has recently been investigated, although results are conflicting. Hypocalcemia, frequently seen in patients with AKI, was found to decrease FGF23 production in rats fed a diet low in calcium despite increased PTH, calcitriol and stable phosphate levels.[38] Subsequent work in genetically modified mice also suggests that hypocalcemia leads to a decrease in FGF23 production in bone.[39] Thus calcium abnormalities cannot account for the changes in FGF23.

Can the increase in FGF23 in hospitalized control patients without AKI yield any clues to the pathophysiology of increased FGF23 in AKI? One study followed prospectively 40 patients undergoing hip replacement.[40] On post-operative day 1 c-terminal FGF23 levels rose in all patients to 2.5-3.2 fold above the pre-operative levels, while intact FGF23 levels did not change and serum phosphate levels were modestly elevated within the normal range. It is possible that c-terminal FGF23 levels uniquely can increase under conditions of stress or inflammation, such as having a surgical procedure. Thus, part of the FGF23 elevation can be due to such stress conditions. However, the intact levels in this study did not change (although they were measured with an assay no longer in use), in contrast to our animal work. Thus the contribution of stressful conditions per se is likely minimal.

Implications for elevated FGF23 in AKI

Can parallels be drawn between the potential adverse effects of elevated FGF23 levels in CKD and AKI (Table 2)? In CKD patients, higher FGF23 levels correlate with higher risk of death and ESRD.[7] In the above admittedly small studies, elevated FGF23 levels correlated with mortality, the composite of death/ need for RRT or with length of ICU stay and length of ventilation.[33-35] Analysis of larger cohorts of patients with AKI is necessary to see if these findings can be replicated. Even if they are, many unanswered questions will still remain regarding causality and potential mechanisms to explain these observations.

The strongest evidence for a potential causal link between elevated FGF23 levels and end-organ damage comes from studies of effects on the heart, where FGF23 injections into heart muscle were shown to cause hypertrophy of myocytes. Might higher levels in AKI predict later development of cardiac hypertrophy? For example, injections of FGF23 into animals with normal renal function to elevate FGF23 levels approximately four-fold over baseline over the course of just five days resulted in significant increase in left ventricular wall thickness and cardiomyocyte hypertrophy.[22] The levels observed in AKI patients are

usually at several-fold above baseline. However, among patients with CKD and elevated FGF23 levels in a CKD cohort, LVH was detected in only 20% of patients after a follow up of three years.[22] Thus, while at least hypothetically, exposure to elevated FGF23 levels during an episode of AKI may have deleterious effects on cardiac myocytes, it may be necessary to have a prolonged exposure in humans to lead to maladaptive remodeling. Certainly the effect of FGF23 within the context of an episode of AKI on hearts and cardiac myocytes needs to be examined in animals.

Conclusion

Acute kidney injury, far from involving just one organ, is a systemic disease that can affect distant organ function acutely (for example leading to lung injury), and, potentially, long-term (for example leading to increased long-term fracture risk in survivors of AKI).[41, 42] The mechanisms or mediators of these effects are far from clear but likely include inflammatory mediators that either directly or indirectly inflict pathological change. It is exciting to try to imagine FGF23 as one of these mediators, since FGF23 has been linked epidemiologically with adverse distant organ effects in CKD and dialysis patients (for example, with cardiovascular mortality) and mechanistically with ventricular hypertrophy.[22] However, much work remains to determine, both epidemiologically and mechanistically, if elevated FGF23 levels during AKI have similar distant organ effects.

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Key points

- FGF23 levels increase rapidly in patients and animals with AKI
- The mechanisms leading to the acute increase in FGF23 likely do not involve regulation by phosphate, calcitriol or PTH, but may be due to a combination of increased production by bone (and other tissues), and reduced clearance
- In small human studies, elevated FGF23 levels correlate with morbidity and mortality

Table 1
Potential etiologies for elevated FGF23 levels in AKI

	Direct evidence	**Hypothesized based on other studies**
Increased production	Increased protein levels in bone	Increased levels in Kidneys AND/OR Increased levels in other organs (co-morbidities)
Decreased removal from circulation	Slower disappearance of injected human FGF23 from mouse circulation	
Altered processing		Increased generation of c-terminal fragment due to functional iron deficiency AND/OR Decreased generation of c-terminal fragment due to uremic inhibition

Table 2
Adverse outcomes associated with elevated FGF23 levels in AKI

Based on small human cohorts with AKI	Hypothesized based on epidemiologic CKD or dialysis patient data
Increased fluid gain	Increased risk for CKD
Longer time on ventilator	Faster progression toward dialysis
Increased mortality or need for dialysis	Increased risk of cardiovascular and/or all cause mortality