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Kidney Clearance of FGF23 in Humans

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Abstract

Purpose of review: Recent studies have shed light on factors influencing FGF23 regulation in terms of its production and cleavage. However, less is known about FGF23 elimination from circulation. The kidney's role in FGF23 elimination will be the focus of this review.

Recent Findings: Marked abnormalities in FGF23 physiology have been observed in persons with reduced kidney function compared to healthy persons and raise the question of whether the kidney may be directly regulating FGF23 concentrations. FGF23 concentrations rise dramatically after onset of acute kidney injury and early chronic kidney disease and are associated with poor clinical outcomes. New studies leveraging measurements of FGF23 in the aorta and renal veins concurrently demonstrate that the human kidney efficiently extracts both intact and C-terminal FGF23 from the circulation independent of kidney function and catabolize the hormone. Additionally, the kidney's reduction of PTH predicts the amount it will reduce both C-terminal and intact FGF23.

Summary: The human kidney removes both intact FGF23 and its C-terminal fragments. FGF23 catabolism within the kidney may be influenced by PTH concentrations, and other factors. Future studies to understand regulation of these hormones and the kidney's role in this interplay are timely.

Keywords

FGF23; Kidney; Clearance; PTH

Introduction

Fibroblast growth factor-23 (FGF23) was initially characterized as a regulator of phosphate homeostasis. Derived mainly from bone osteocytes, it functions to lower serum phosphate

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concentrations by promoting kidney phosphate excretion and reducing the synthesis of 1,25-dihydroxyvitamin D. The inhibition of 1,25-dihydroxyvitamin D synthesis secondarily further lowers serum phosphate concentrations by limiting intestinal phosphate absorption. FGF23 concentrations rise early in chronic kidney disease (CKD), and generally precede changes in other mineral metabolites.[1] It is widely hypothesized that these early increases in FGF23 concentrations occur initially as an adaptive response, setting forward a cascade of 1,25-dihydroxyvitamin D suppression and parathyroid hormone (PTH) elevation that work in concert to maintain phosphate concentrations in the normal range despite lower nephron mass.[2] Since the discovery of FGF23 and its identification as a key factor in the regulation of phosphate homeostasis, its physiology has been intimately linked to the kidney. This is both through the marked abnormalities in FGF23 physiology observed in persons with reduced kidney function, and, albeit less studied, through the kidney's direct role in maintaining FGF23 concentrations. The kidney's role in this intricate interplay will be the focus of this review.

While FGF23 concentrations are associated with adverse clinical outcomes including heart failure, cardiovascular events, and mortality across the spectrum of CKD severity, associations appear particularly strong in persons with end stage kidney disease. Associations are typically,[3–5] but not always,[6] found to be independent of other markers of mineral metabolism and kidney function. In persons with kidney failure receiving maintenance dialysis, FGF23 concentrations are often 1,000-fold higher than seen in healthy persons,[7] and subtle early abnormalities in kidney function frequently already manifest with FGF23 elevations. In our early studies, we found that estimated glomerular filtration rate (eGFR) levels as modest as <85ml/min/1.73m^2 were already sufficient to lead to higher FGF23 concentrations, and that low-grade albuminuria with preserved GFR was also associated with higher FGF23 concentrations.[8] These findings raise the question of whether the kidney may be directly regulating FGF23 concentrations, perhaps simply by retaining FGF23 due to decreased clearance, perhaps through direct metabolism, or perhaps a combination of both of these mechanisms.

Early Recognition of FGF23 Regulation by the Kidney

Early support for the hypothesis that the kidney directly regulates FGF23 concentrations came from rodent studies, as plasma FGF23 concentrations were found to rise early and dramatically after onset of acute kidney injury (AKI) in murine models of folic acid and pigment nephropathy.[9] In humans, evidence of the kidney's role in FGF23 metabolism also first emerged in studies of AKI. In patients undergoing cardiac surgery, FGF23 concentrations differentially increased after cardiopulmonary bypass in patients with AKI compared to those without AKI. Importantly, fragments of FGF23 were detected in the urine of these AKI patients, indicative of potential kidney catabolism,[10] and both urine and plasma FGF23 concentrations associated with death, suggesting that this catabolic pathway may be clinically important. The elevations in plasma FGF23 concentrations with AKI were later confirmed in a post-hoc analyses of patients with acute lung injury with additional demonstration of risk of 60-day mortality in patients with higher plasma FGF23.[11]

The direct role of the kidney in removing FGF23 from circulation in humans was demonstrated in an elegant study by Van Ballegooijen and colleagues. The investigators evaluated 17 humans undergoing coronary angiography where blood specimens were simultaneously sampled in the aorta and renal vein. They demonstrated that intact FGF23 concentrations were 17% lower in the renal vein relative to the aorta. The investigators also measured FGF23 in urine, finding very low concentrations, thereby suggesting that most of the 17% of FGF23 removed from circulation by the kidneys was metabolized in the kidney rather than excreted.[12] Based on their data, we estimated FGF23 clearance using UV/P to be approximately 0.2ml/min, much lower than one would anticipate by a 17% kidney reduction from aorta to renal vein with normal renal plasma flow, as a 17% reduction approximates the single pass renal creatinine clearance, and therefore would suggest a kidney clearance of FGF23 of approximately 100ml/min. This large discrepancy is likely explained by kidney metabolism. This study therefore not only directly demonstrated that the kidney removed intact FGF23 from circulation, but that much of the extracted FGF23 was metabolized by the kidney.

FGF23 Biology

So far, we have discussed FGF23 as a single moiety, however its biology is more complex, as both the intact FGF23 hormone, and its C-terminal fragments are measurable in humans and are under distinct biological control. FGF23 is initially translated into a 251-amino acid peptide and, following the removal of a 24 amino acid (AA) N-terminal signaling peptide, the mature 227 AA hormone, often referred to as “intact” FGF23 is available for secretion into the circulation from bone osteocytes. Alternatively, under the regulation by glycosylation and phosphorylation at key residues, intact FGF23 can be cleaved during post-translational modification into fragments.[13] There are two main types of assays for measuring FGF23 in humans. Intact assays utilize antibodies that capture epitopes on either side of the FGF23 cleavage site, thus they detect only intact, biologically active FGF23.[14] The C-terminal assay recognizes two epitopes on the C-terminus aspect of the hormone, capturing both intact FGF23 and its C-terminal fragments,[15] thus corresponding to total FGF23. Although biological activity of intact FGF23 is well documented, novel actions of the carboxy terminal fragments of FGF23 have also recently been reported.[16] Relative abundance of C-terminal FGF23 fragments versus intact FGF23 varies by the severity of eGFR reductions in humans. In individuals with normal kidney function, while levels of total FGF23 (as measured by the C-terminal assay) and intact FGF23 are relatively low compared to persons with kidney failure, total FGF23 concentrations (as measured by the C-terminal assay) tend to be higher relative to intact FGF23 concentrations. However, as CKD progresses, while there is an increase in both intact and total FGF23 (measured by C-terminal assay), their relative abundance becomes more similar to one another.[17] The reason for these changes in relative abundance in relation to kidney function remain uncertain.

Concurrently, novel insights into the effects of iron deficiency and inflammation have demonstrated unique pathways that regulate FGF23 cleavage. Iron deficiency and systemic inflammation upregulate both FGF23 production and its cleavage in the osteocyte, such that total FGF23 concentrations (as measured by C-terminal assay) are high but the concentrations of intact FGF23 are either within the normal range or only slightly increased

in persons with iron deficiency or inflammation.[18] It has also been hypothesized that CKD leads to accumulation of an unidentified inhibitor of FGF23 cleavage.[19] An alternative, previously untested hypothesis is that the kidney itself may have differential clearance of intact FGF23 and its C-terminal fragments.

Clearance of Intact FGF23 and its C-terminal Fragments

Based on these data, we hypothesized that the kidney may have differential clearance of intact FGF23 and C-terminal fragments. We recently measured intact FGF23 and total FGF23 concentrations (as measured by C-terminal assay) in the aorta and bilateral renal veins of 162 patients with essential hypertension undergoing renal angiography. The mean eGFR was 72 ± 48 ml/min/100g and 44 (27%) had CKD (eGFR < 60ml/min/1.73m^2). We found that the human kidney reduced the concentrations of both total FGF23 (16% ± 12%) and intact FGF23 (21% ± 16%), but that the kidney's clearance of intact FGF23 was higher ($p< 0.001$) than for total FGF23 concentrations (as measured by C-terminal assay). ** [20] The greater kidney reduction of intact FGF23 compared to total FGF23 appeared stable and consistent across the range of eGFR we evaluated. As the C-terminal FGF23 assay measures both the intact hormone and cleaved C-terminal fragments, this finding suggests that the human kidney may be more effective at clearing the intact FGF23 hormone than smaller fragments (Figure 1). The finding that the kidney clearance of both moieties remained consistent across the range of eGFR we tested also argues strongly against the hypothesis that differential kidney clearance explains the change in relative abundance as GFR declines. Our findings support previous studies where urinary clearance of total FGF23 were not thought to be the leading causes of elevation in its serum concentrations.[21, 22]

Interactions with Parathyroid Hormone

While our study gives direct evidence to the kidney's role of clearance of both intact FGF23 and its C-terminal fragments in humans, it also raised new questions about the kidney's direct role in PTH-FGF23 regulation. We observed that the kidney's reduction of PTH predicted the amount it would reduce both total and intact FGF23. This relationship was independent of kidney function. Prior studies have demonstrated that FGF23 is in a negative feedback loop with PTH. FGF23 has a direct inhibitory effect on the parathyroid gland by decreasing the expression and protein secretion of PTH.[23, 24] On the other hand, PTH can stimulate the secretion of FGF23 by osteoblasts in rodent models of hyperparathyroidism. This effect is reversed after parathyroidectomy.[25,26] This feedback loop between the parathyroid and bone did not consider the potential role of the kidneys in catabolism of PTH and FGF23. As we found that the amount of PTH extraction by the kidney is strongly related to the amount of FGF23 extraction in the kidney, independent of eGFR, this raises the possibility that the simple negative feedback loop between the parathyroid gland and bone may be too simplistic. PTH may also be influencing FGF23 catabolism within the kidney. However, while intriguing, and a strong independent relationship of PTH clearance predicted FGF23 clearance, the cross-sectional study design renders it unclear whether PTH kidney extraction may drive FGF23 extraction or vice versa (Figure 2), or perhaps whether a third factor induces greater kidney extraction of both concurrently. Future studies designed to manipulate one or the other hormone and examine the kidney's responses are needed to investigate the direction of this new interaction.

Conclusion

Exciting biological discoveries continue to provide new insights into mechanisms that regulate intact FGF23 and its C-terminal fragments, and the consequences of their concentrations to health and disease. While much progress has been made to understand factors influencing FGF23 production and cleavage in bone, and its regulation by iron deficiency, inflammation, and other hormones including PTH and $1,25(OH)_2$ vitamin D, much less attention has been given to how FGF23 is eliminated from the circulation. New studies leveraging measurements of FGF23 in the aorta and renal veins concurrently have now demonstrated that the human kidney efficiently extracts both intact FGF23 and C-terminal fragments from the circulation and catabolize the hormone. A new and exciting chapter awaits, as it may be hypothesized that the efficiency of the kidney in clearing FGF23 may be potentially influenced by PTH concentrations, and perhaps other hormones. Future studies are needed to understand not only the role of these hormones in regulating one another in production and release into the circulation by the parathyroid gland and bone, but also on the kidney's role in this complex interplay. Finally, given the substantial role of the kidney in FGF23 catabolism, a holistic understanding of the regulation of FGF23 will require additional research not only into its production and cleavage, but also in its elimination.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

References

1. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. 2011;79(12):1370–1378. [PubMed: 21389978]
2. Larsson T, Nisbeth U, Ljunggren O, et al. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney Int. 2003;64(6):2272–9. [PubMed: 14633152]
3. Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–592. [PubMed: 18687639]
4. Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. 2011;305(23):2432–2439. [PubMed: 21673295]
5. Parker BD, Schurgers LJ, Brandenburg VM, et al. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. Ann Intern Med. 2010;152(10):640–648. [PubMed: 20479029]

6. Sharma S, Katz R, Bullen AL, Chaves PHM, de Leeuw PW, Kroon AA, Houben AJHM, Shlipak MG, Ix JH. Intact and C-Terminal FGF23 Assays-Do Kidney Function, Inflammation, and Low Iron Influence Relationships With Outcomes? J Clin Endocrinol Metab. 2020;105(12):4875–85.
7. Gao S, Xu J, Zhang S, Jin J. Meta-Analysis of the Association between Fibroblast Growth Factor 23 and Mortality and Cardiovascular Events in Hemodialysis Patients. Blood Purif. 2019; 47 Suppl 1(Suppl 1):24–30. [PubMed: 30699419]
8. Ix JH, Katz R, Kestenbaum BR, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). J Am Coll Cardiol. 2012;60(3):200–207. [PubMed: 22703926]
9. Christov M, Waikar SS, Pereira RC, et al. Plasma FGF23 levels increase rapidly after acute kidney injury. Kidney Int. 2013;84(4):776–785. [PubMed: 23657144]
10. Leaf DE, Jacob KA, Srivastava A, et al. Fibroblast Growth Factor 23 Levels Associate with AKI and Death in Critical Illness. J Am Soc Nephrol. 2017;28(6):1877–1885. [PubMed: 28028134]
11. Leaf DE, Siew ED, Eisenga MF, et al. Fibroblast Growth Factor 23 Associates with Death in Critically Ill Patients. Clin J Am Soc Nephrol. 2018;13(4):531–541. [PubMed: 29519954]
12. van Ballegooijen AJ, Rhee EP, Elmariah S, de Boer IH, Kestenbaum B. Renal Clearance of Mineral Metabolism Biomarkers. J Am Soc Nephrol. 2016;27(2):392–397. [PubMed: 26047790]
13. Ichikawa S, Gray AK, Padgett LR, et al. Genetic rescue of glycosylation-deficient Fgf23 in the Galnt3 knockout mouse. Endocrinology. 2014;155(10):3891–3898. [PubMed: 25051439]
14. Shimada T, Urakawa I, Isakova T, et al. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. J Clin Endocrinol Metab. 2010;95(2):578–585. [PubMed: 19965919]
15. Jonsson KB, Zahradnik R, Larsson T, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med. 2003;348(17):1656–1663. [PubMed: 12711740]
16. Berndt TJ, Craig TA, McCormick DJ, et al. Biological activity of FGF-23 fragments. Pflugers Arch. 2007;454(4):615–623. [PubMed: 17333246]
17. Smith ER, Cai MM, McMahon LP, Holt SG. Biological variability of plasma intact and C-terminal FGF23 measurements. J Clin Endocrinol Metab. 2012;97(9):3357–3365. [PubMed: 22689697]
18. Babitt JL, Sitara D. Crosstalk between fibroblast growth factor 23, iron, erythropoietin, and inflammation in kidney disease. Curr Opin Nephrol Hypertens. 2019;28(4):304–310. [PubMed: 31145704]
19. Stubbs JR, He N, Idiculla A, et al. Longitudinal evaluation of FGF23 changes and mineral metabolism abnormalities in a mouse model of chronic kidney disease. J Bone Miner Res. 2012;27(1):38–46. [PubMed: 22031097]
20. Sharma S, Katz R, Ginsberg C, et al. Renal Clearance of Fibroblast Growth Factor-23 (FGF23) and its Fragments in Humans. J Bone Miner Res. 2022;37(6):1170–1178. [PubMed: 35373859] ** In this cross-sectional study of patients with essential hypertension, authors demonstrated that the human kidney extracted both intact FGF23 and its fragments from the circulation, and this was independent of kidney function.
21. Larsson T, Nisbeth U, Ljunggren O, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney Int. 2003 Dec;64(6):2272–9. [PubMed: 14633152]
22. Isakova T, Xie H, Barchi-Chung A, Vargas G, Sowden N, Houston J, Wahl P, Lundquist A, Epstein M, Smith K, Contreras G, Ortega L, Lenz O, Briones P, Egbert P, Ikizler TA, Jueppner H, Wolf M. Fibroblast growth factor 23 in patients undergoing peritoneal dialysis. Clin J Am Soc Nephrol. 2011 Nov;6(11):2688–95. [PubMed: 21903990]
23. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, et al. The parathyroid is a target organ for FGF23 in rats. J Clin Invest. 2007;117(12):4003–4008. [PubMed: 17992255]
24. Krajisnik T, Bjorklund P, Marsell R, et al. Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. J Endocrinol. 2007;195(1):125–131. [PubMed: 17911404]

25. Kawata T, Imanishi Y, Kobayashi K, et al. Parathyroid hormone regulates fibroblast growth factor-23 in a mouse model of primary hyperparathyroidism. J Am Soc Nephrol. 2007;18(10):2683–2688. [PubMed: 17855636]

26. Carrillo-Lopez N, Panizo S, Alonso-Montes C, et al. High-serum phosphate and parathyroid hormone distinctly regulate bone loss and vascular calcification in experimental chronic kidney disease. Nephrol Dial Transplant. 2019;34(6):934–941. [PubMed: 30189026]

Key points

1. Human kidney removes both intact FGF23 and its C-terminal fragments independent of estimated glomerular filtration rate.
2. Kidney's reduction of parathyroid hormone predicts the amount it would reduce both intact FGF23 and its C-terminal fragments independent of estimated glomerular filtration rate.
3. Future studies are needed to examine the potential role of the kidney in regulation and clearance of FGF23 and parathyroid hormone, and their interaction.

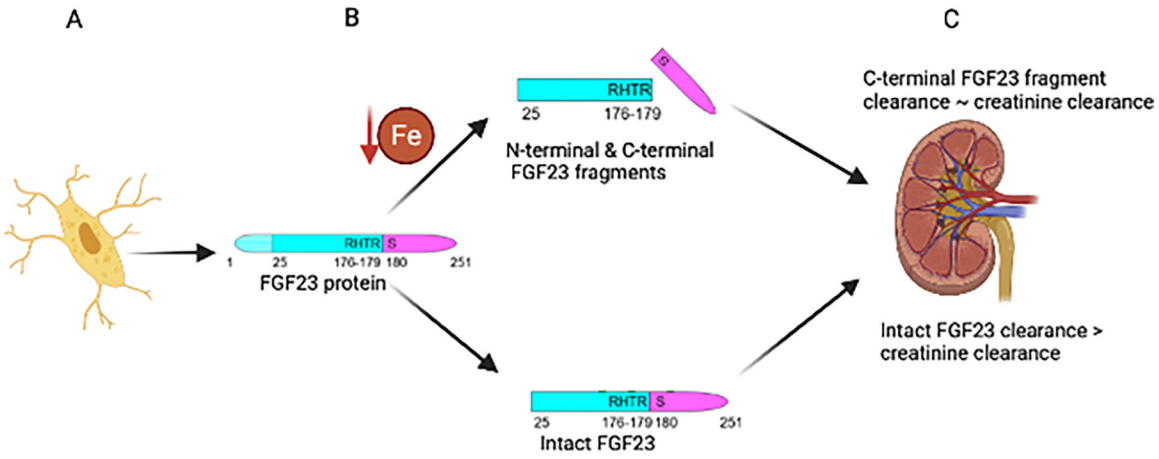

Figure 1:

FGF23 Production, Cleavage and Kidney Clearance. (A) FGF23 protein is produced as a peptide with 251 amino acids. (B) FGF23 with 227 amino acids is secreted after the cleavage of a signal peptide with 24 amino acid. Part of FGF23 protein is cleaved into N-terminal and C-terminal fragments. Iron deficiency, inflammation and erythropoietin stimulate FGF23 production and cleavage. (C) Human kidney clears both intact FGF23 and its C-terminal fragments. The kidney's clearance of intact FGF23 is higher than C-terminal FGF23, whereas clearance of C-terminal FGF23 is similar to creatinine clearance.

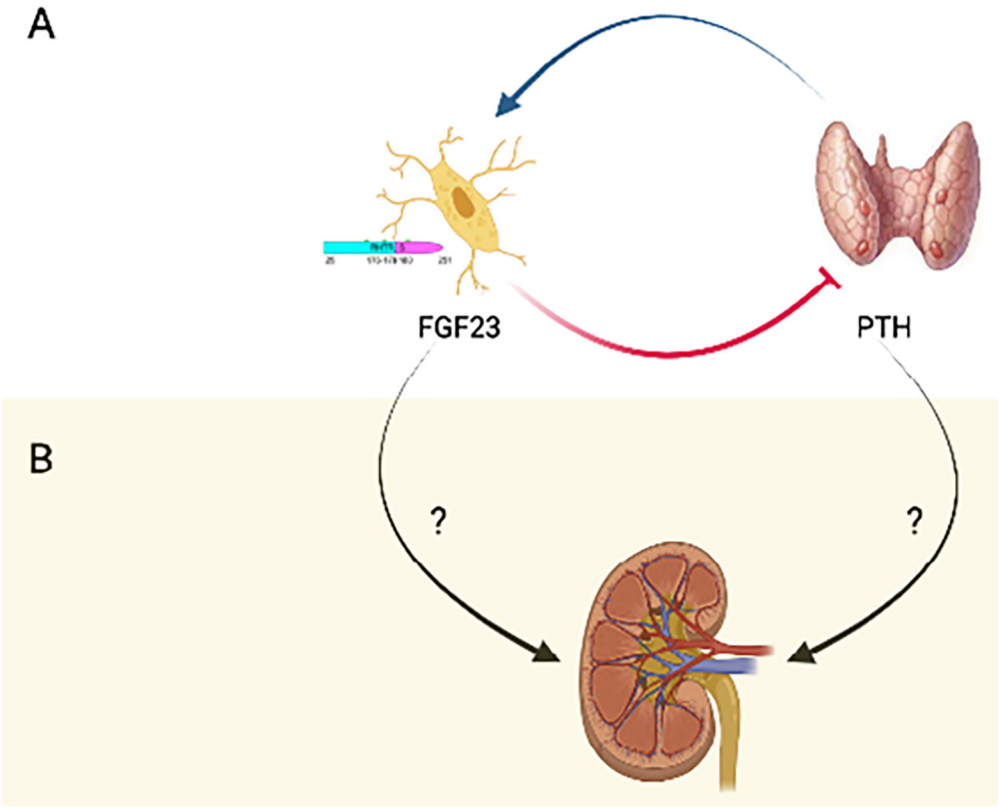

Figure 2:
FGF23, Parathyroid hormone (PTH) and the Kidney Clearance. (A) Known regulation of FGF23 and PTH. Red line indicates inhibition; Blue arrow indicates stimulation. (B) Hypothesized relationship between FGF23 and PTH clearance through the human kidney. FGF23 kidney extraction may drive PTH extraction or vice versa or an unknown factor may induce greater kidney extraction of both concurrently.