Fibroblast Growth Factor 23 and Pro-B-Type Natriuretic Peptide as a Risk factor of Cardiac Hypertrophy in Chronic Kidney Disease

Amal Mohamed Abd El-Latef [1], Hany El-Sayed Ibrahim [1], Saad Sabry Osh [2], Mona Mohamed Morsy Mohamed [1]

1 Pediatric Department, Faculty of Medicine, Zagazig University, 2 Clinical Pathology Department, Faculty of Medicine, Zagazig University

Corresponding author: Amal Mohamed Abd El-Latef

Conflict of interest: None declared.

Funding: No funding sources

Abstract

Cardiac hypertrophy is a life-threatening disorder and is frequently observed in patients with chronic kidney disease (CKD). Much attention has been focused on the derangement in hormonal factors, including FGF23, as a novel cause of cardiac hypertrophy in CKD. Recently, FGF23 is shown to be elevated as CKD progresses and may be responsible for the development of cardiac hypertrophy and heart failure. Furthermore, FGF23 not only inhibits the renal expression of angiotensin converting enzyme 2 but also enhances renin gene transcription, both of which could accelerate renin-angiotensin-aldosterone system. Although the increase in serum phosphate concentrations is a pivotal stimulus for FGF23 production, recent studies suggest that reduced iron status and elevated aldosterone levels, frequently seen in patients with CKD or on dialysis, might also contribute to the elevation in serum FGF23 levels. Conversely, phosphate binders and appropriate iron status could reduce serum FGF23, potentially leading to the alleviation of cardiac hypertrophy and heart failure. Also, it was hypothesized that N-terminal pro–B-type natriuretic peptide (NT–pro-BNP) and B-type natriuretic peptide (BNP) levels could identify CAD and LVH in asymptomatic patients with CKD. In conclusion, novel therapeutic strategies associated with FGF23 may confer a benefit in the management of cardiac disorders in CKD.

Keywords: Cardiac Hypertrophy, Chronic Kidney Disease, Pro-BNP, FGF23

Regul Sci. ™ 2023; 9(1): 8922 - 8929

DOI: doi.org/10.18001 /TRS.9.1. 637

Introduction

Chronic kidney disease (CKD) is a life-threatening disorder and relentlessly progresses to end-stage kidney disease requiring renal replacement therapy. A growing body of evidence has been accumulated that CKD is closely associated with increased risk of cardiovascular events and death.

Go et al., (1) demonstrated that the event rate inversely parallels the level of renal function. Likewise, cardiovascular events are associated with the reduction in glomerular filtration rate (GFR) among Japanese population **(2, 3)**. Cardiovascular disease observed in CKD includes a variety of disorders such as heart failure and cardiac hypertrophy. Since cardiac hypertrophy per se is more prevalent as renal function deteriorates and reflects an ominous outcome with increased mortality **(4)**, the alleviation of this disorder would offer improved survival to CKD patients.

Although hemodynamic derangement such as systemic hypertension and volume overload plays a major role in the development of cardiac hypertrophy, several lines of recent studies indicate that humoral factors also contribute to the development of cardiac hypertrophy. For example, angiotensin II is a well-known factor that exerts direct hypertrophic action on cardiomyocytes **(5)**. Further evidence has accrued that aldosterone, a traditional hormone regulating serum electrolyte balance, not only induces renal glomerular hypertension **(6)** but also causes cardiac hypertrophy **(7)** and heart failure. Because such humoral factors are often elevated in CKD **(8)**, the strategy to counter the action of these factors would improve various perturbed conditions in CKD and is currently proposed as a milestone treatment of CKD, particularly with the use of renin-angiotensin system (RAS) inhibitors **(9).**

It is well recognized that CKD is accompanied by a variety of disturbance of the internal milieu, including electrolyte disorders. Despite impaired ability of renal excretory function, serum phosphate levels remain relatively unchanged until GFR falls below half of the normal level. Recent studies disclose that fibroblast growth factor 23 (FGF23) contributes importantly to the regulation of the serum phosphate concentration by inhibiting the phosphate reabsorption in the proximal tubule, which mitigates the tendency toward phosphate retention in CKD **(10).** Although this mechanism teleologically serves to act as an adaptive regulatory factor to maintain serum phosphate levels constant, further deterioration of CKD causes the elevation in serum phosphate concentrations, which hence would stimulate FGF23 production. Furthermore, of importance is the finding that elevated serum FGF23 concentrations are associated with the development of cardiac disorders **(11)**. Thus, apparently homeostatic mechanism for phosphate metabolism may act to aggravate cardiac disease, leading to cardiac hypertrophy and heart failure.

FGF23 and phosphate in CKD

FGF23 is identified as a glycoprotein hormone that has been discovered as a member of the FGF family **(12)**. The subsequent investigations have unveiled an important role of FGF23 in the homeostatic mechanism of serum phosphate levels. The conventional hypothesis, i.e., "trade-off theory" **(13)**, where secondary hyperparathyroidism is assumed to play a central role in phosphate metabolism in CKD, therefore, has been updated by the introduction of FGF23 to the concept of the phosphate metabolism in CKD.

Serum FGF23 levels have been shown to rise at early stages of CKD. Several studies demonstrate that serum FGF23 is elevated even prior to the stage when serum parathyroid hormone rises **(14).** Although the precise cellular mechanisms for the release and synthesis of FGF23 remain fully undetermined, the elevation in serum phosphate and parathyroid hormone constitute determinants that trigger the release of FGF23 from osteocytes and osteoblasts (Fig. 1). Because FGF23 is a potent phosphaturic hormone that inhibits phosphate reabsorption through Na/P cotransporter 2a/c in the proximal tubule **(15)**, FGF23 would serve to mitigate hyperphosphatemia

entailing impaired renal function. FGF23 also suppresses vitamin D activity by inhibiting renal 1α-hydroxylase (the enzyme that converts 25-hydroxyvitamin D3 to its active form) and stimulating 24-hydroxylase (the enzyme degrading to inactive form), leading to the decrease in phosphate and calcium absorption from the intestine. Although FGF23 can inhibit parathyroid hormone production, the effects of suppressed vitamin D activity along with decreased Ca levels would govern the serum parathyroid hormone level more robustly in CKD, which results in elevated parathyroid hormone levels characteristics of the hormonal profiles seen in CKD patients **(16, 17).**

FGF23 and sodium in CKD

In addition to the phosphaturic action in renal proximal tubules, FGF23 is found to exert sodium retaining action in distal tubular segments. Thus, **Andrukhova et al., (18)** have recently demonstrated that FGF23 upregulates the sodium chloride cotransporter (NCC) in distal tubules, which conceivably results in systemic volume expansion and hypertension. This finding encompasses an important issue because FGF23 could cause the suppression of RAS due to systemic volume expansion and subsequently decrease plasma aldosterone levels **(19)**. In contrast, a positive correlation between FGF23 and aldosterone concentrations is also reported in patients with CKD and heart failure **(20)**. In this regard, CKD is demonstrated to be associated with decreased renal expression of Klotho **(21-26)**. Since the action of FGF23 on NCC requires the integrity of the FGF receptor/Klotho complex, the ability of FGF23 to promote sodium retention and the subsequent development of hypertension may depend on intact FGF receptor/Klotho complex activity. Indeed, the observation that plasma aldosterone levels are elevated in advanced CKD suggests the diminished ability of elevated FGF23 to induce volume expansion, possibly due to reduced Klotho expression in the kidney.

FGF23 and cardiac hypertrophy

Cardiac hypertrophy is a critical complication that is frequently observed in CKD **(27)**. Cardiac hypertrophy develops beginning at early stages of CKD and is quite common in patients on dialysis therapy. In addition to the traditional determinants causing cardiac hypertrophy, including hypertension, renin-angiotensin system, and chronic anemia, aldosterone is also established as a crucial factor for cardiac hypertrophy. Furthermore, parathyroid hormone is suggested as a cause of cardiac hypertrophy in dialysis patients **(28)**, although contradictory results are also reported **(29)**. Of interest, mineralocorticoid receptor blockade reduces serum parathyroid hormone levels in normal subjects as well as in patients with CKD and heart failure, suggesting that aldosterone stimulates parathyroid hormone production **(30, 31)**. Alternatively, parathyroid hormone enhances the aldosterone secretion from adrenal cortex. Clinical implications of these interactions in the development of cardiac hypertrophy, however, remain undetermined **(32)**.

More recently, much attention has been focused on the role of FGF23 since this substance not only participates in the phosphate homeostasis but also induces cardiac hypertrophy (Table 3). Thus, **Gutierrez et al., (33)** discovered that there existed a close relationship between serum FGF23 levels and LV mass index in patients with CKD. **Faul et al., (34)** also demonstrated that LV mass index was increased as serum FGF23 levels were elevated. This relationship was also observed in patients on maintenance hemodialysis. Finally, intravenous injection of FGF23 caused

cardiac hypertrophy in mice, and the administration of an FGF receptor antagonist (PD173074) prevented the development of the CKD (i.e., 5/6 nephrectomy)-induced cardiac hypertrophy. Of importance, elevated serum FGF23 levels are causally linked to reduced ejection fraction. Collectively, these observations provide conclusive evidence for the role of FGF23 in the development of cardiac disorders in CKD.

Table 1 FGF23 and cardiac hypertrophy in CKD

Authors	*n*	Effects of FGF23 on cardiac hypertrophy
Humans		
Gutierrez OM et al.	162 CKD	Incidence of LVH (%), FGF23 < 75 RU/ml; 7%, 75–150 RU/ml, 21%, > 150 RU/ml; 25%
Faul C et al.	3070 CKD	Incidence of LVH (eccentric+concentric)%, FGF23 quarfile 1; 38%, quarfile 2; 45%, quartile 3; 54%, quarfile 4; 70%
Hsu HJ et al.	124 hemodialysis	Serum FGF23 level is independently associated with LVH in hemodialysis patients
Seifert Me et al.	31 CKD stage 3	The change in FGF23/klotho ratio was strongly correlated with changes in LV mass index.
Sarmento-Dias M et al.	48 peritoneal dialysis	In multivariate adjusted analysis, FGF23was associated with LVMI ($\beta = 0.298$, $p = 0.041$),
Javanovich A et al.	2255 elderly CKD	Higher FGF23 concentrations were associated with greater LVM in adjusted analyses ($\beta = 6.71$ [95% CI 4.35–9.01] g per doubling of FGF23).
Tanaka S. et al	903 CKD stage 1 to 5	The correlation between FGF23 and LVMI was significant among those with CKD stage G1/G2, G3a, and G4.
Chue CD. et al	120 CKD stage 3	Sevelamer carbonate reduced FGF23 but failed to improve LV mass
Animals		
Maizel J et al.	CKD mice	Sevelamer reduced serum phosphate and LV hypertrophy but not FGF23.
Yamazaki-Nakazawa A et al.	CKD rats	Lanthanum carbonate reduced LV weight but failed to decrease FGF23 levels.

Although a growing body of evidence has been accumulated regarding the role of FGF23 in cardiac hypertrophy in CKD, the mechanism responsible for the cardiac disorder remains undetermined fully. In experimental models of mice, **Faul et al., (34)** demonstrated that the FGF23-induced cardiac hypertrophy was abrogated by a phospholipase Cγ inhibitor (U73122) and a calcineurin inhibitor (cyclosporine A), but not by a MAP kinase inhibitor (PD98059), a PI3 kinase inhibitor (wartmannin), or an Akt inhibitor (A6730). Furthermore, pan FGF receptor blockade by PD173074 reduced LV mass and the cardiac expression of genes associated with LV hypertrophy **(35)**, and the receptor involved was identified as FGF receptor 4 **(36)**. These findings lend support to the premise that FGF23-induced cardiac hypertrophy is mediated by the FGF receptor 4/PLCγ/calcineurin pathway.

N-Terminal Pro-B-Type Natriuretic Peptide for Identifying Left Ventricular Hypertrophy in Chronic Kidney Disease

The **Khan et al. (37)** study demonstrates that in ambulatory patients with CKD not requiring dialysis, NT–pro-BNP and BNP can identify, with similar accuracy, patients with LVH and CAD. Serum levels of NT–pro-BNP and BNP generally increase with worsening renal impairment **(38).**

Furthermore, it has been hypothesized that NT–pro-BNP may be more dependent on renal clearance than BNP, limiting the diagnostic accuracy of the test in this setting. The results indicate a greater increase in NT–pro-BNP levels compared with BNP levels from the established reference ranges **(39).**

Consistent with the finding that natriuretic peptide levels are in large part independent of renal function is the absence of a progressive trend in the prevalence of LVH or CAD by progressive stages of CKD. Although long-term outcome studies are still needed in the CKD population to determine if natriuretic peptides can specifically predict adverse cardiac events, the ability of NT–pro-BNP and BNP to identify CAD and LVH suggests that elevated levels may be a method for identifying CKD populations at the highest cardiovascular risk **(40).**

The elevated levels of natriuretic peptides in renal failure could be due to a combination of real insufficiency and the presence of underlying cardiac disease. In such cases, renal insufficiency will increase the optimal level of a marker for the prediction of cardiac disease **(41).**

Conclusions

Cardiac hypertrophy is a serious complication observed frequently in patients with CKD. Among multiple factors involved in cardiac disease, humoral factors, including FGF23, are gaining much attention as critical components responsible substantially for the development of cardiac hypertrophy and heart failure that lead to increased morbidity and mortality. Recent progresses in the therapeutic strategies using novel tools facilitate the management of CKD. Novel approaches from the standpoint of hormonal (FGF23) and mineral/electrolyte factors (phosphate) as well as iron status appear to be a promising strategy and could constitute a mainstay in the treatment of cardiovascular disorders in CKD. Elevated natriuretic peptide levels are common in patients with chronic kidney disease (CKD), as is the presence of coronary artery disease (CAD) and left ventricular hypertrophy (LVH).

References:

1. Go AS, Chertow GM, Fan D, et al. Cheonic kidney disease and the cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.

2. Ninomiya T, Kiyohara Y, Tokuda Y, et al. Japan arteriosclerosis longitudinal Study Group. Impact of kidney disease and blood pressure on the development of cardiovascular disease: an overview from the Japanese Longitudinal Study. Circulation 2008; 118: 2694-2701.

3. Tanaka K, Watanabe T, Takeuchi A, et al. CKD-JAC Investigators. Cardiovascular events and death in Japanese patients with chronic kidney disease. Kidney Int 2017; 91:227-234.

4. Dubin RF, Deo R, Bansal N, et al. Associations of conventional echocardiographic measures with incident heart failure and mortality: the chronic renal insufficiency cohort. Clin J Am Soc Nephrol. 2017;12:60–8.

5. Nishida M, Tanabe S, Maruyama Y, et al. Gα12/13- and reactive oxygen species-dependent activation of c-Jun NH2-terminal kinase and p38 MAPK by angiotensin receptor stimulation in rat neonatal cardiomyocytes. J Biol Chem. 2015;280:18434–41.

6. Nagase, M., & Fujita, T. (2008). Aldosterone and glomerular podocyte injury. Clinical and experimental nephrology, 12, 233-242.

7. Sato A, Hayashi K, Naruse M, et al. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension. 2003;41:64–8.

8. Hosoya K, Minakuchi H, Wakino S, et al. Insulin resistance in chronic kidney disease is ameliorated by spironolactone in rats and humans. Kidney Int. 2015;87:749–60.

9. Saruta T, Hayashi K, Ogihara T, et al. Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: subanalysis of the CASE-J study. Hypertens Res. 2009;32:505–12.

10. Evenepoel, P., Meijers, B., Viaene, L., Bammens, B., Claes, K., Kuypers, D., ... & Vanrenterghem, Y. (2010). Fibroblast growth factor-23 in early chronic kidney disease: additional support in favor of a phosphate-centric paradigm for the pathogenesis of secondary hyperparathyroidism. Clinical journal of the American Society of Nephrology, 5(7), 1268-1276.

11. Hamano T, Sakaguchi Y, Fujii N, et al. Clinical features of CKD-MBD in Japan: cohort studies and registry. Clin Exp Nephrol. 2017;21(Suppl 1):9–20.

12. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF 23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A. 2001;98:6500–5.

13. Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of calcium, phosphorus, and magnesium dysregulation in chronic kidney disease. Semin Dial. 2015;28:564–77.

14. 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;79:1370–8.

15. Tomoe Y, Segawa H, Shiozawa K, et al. Phosphaturic action of fibroblast growth factor 23 in Npt2 null mice. Am J Physiol. 2010;298:F1341-50.

16. Kovesdy CP, Quarles LD. FGF23 from bench to bedside. Am J Phys. 2016;310:F1168–74.

17. Ritter CS, Slatopolsky E. Phosphate toxicity in CHD: the killer among UA. Clin J Am Soc Nephrolo. 2016;11:1088–100.

18. Andrukhova O, Slavic S, Smorodchenko A, et al. FGF23 regulates renal sodium handling and blood pressure. EMBO Mol Med. 2014;6:744–59.

19. Tsai MH, Leu JG, Fang YW, et al. High fibroblast growth factor 23 levels associated with low hemoglobin levels in patients with chronic kidney disease stages 3 and 4. Medicine. 2016;95:e3049. https://doi.org/10.1097/MD.0000000000003049.

20. Imazu M, Takahama H, Asanuma H, et al. Pathophysiological impact of serum fibroblast growth factor 23 in patients with non-ischemic cardiac disease and early chronic kidney disease. Am J Phys. 2014;307:H1504–11.

21. Hu MC, Kuro-o M, Moe OW. Klotho and chronic kidney disease. Contrib Nephrol. 2013;180:47–63.

22. de Seigneux S, Courbebaisse M, Rutkowski JM, Wilhelm-Bals A, et al. Proteinuria increases plasma phosphate by altering its tubular handling. J Am Soc Nephrol. 2015;26:1608–18.

23. De Borst MH, Vervloet MG, ter Wee PM, et al. Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF23-klotho in chronic kidney disease. J Am Soc Nephrol. 2011;22:1603–9.

24. Dai B, David V, Martin A, et al. A Comparative Transcriptome Analysis Identifying FGF23 Regulated Genes in the Kidney of a Mouse CKD Model. PLoS One. 2012;7:e44161.

25. Varaqic J, Ahmad S, Nagata S, Ferrario CM. ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. Curr Hypertens Rep. 2014;16:420.

26. Zhang B, Umbach AT, Chen H, et al. Up-regulation of FGF23 release by aldosterone. Biochem Biophy Res Commun. 2016;470:384–90.

27. Di Lullo L, Gorini A, Russo D, et al. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. Cardiorenal Med. 2015;5:254–66.

28. Hayashi T, Joki N, Tanaka Y, et al. Anaemia and early phase cardiovascular events on haemodialysis. Nephrology (Carlton). 2015;20(Suppl 4):1–6.

29. Randon, R. B., Rohde, L. E., Comerlato, L., Ribeiro, J. P., & Manfro, R. C. (2005). The role of secondary hyperparathyroidism in left ventricular hypertrophy of patients under chronic hemodialysis. Brazilian journal of medical and biological research, 38, 1409-1416.

30. Hassan M, Qureshi W, Sroujieh LS, et al. Interplay of parathyroid hormone and aldosterone antagonist in prevention of heart failure hospitalizations in chronic kidney disease. J Renin-Angiotensin-Aldosterone Syst. 2014;15:278–85.

31. Brown JM, Williams JS, Luther JM, et al. Human interventions to characterize novel relationships between the renin-angiotensin-aldosterone system and parathyroid hormone. Hypertension. 2014;63:273–80.

32. Tomaschitz A, Ritz E, Pieske B, et al. Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease. Metabolism Clin & Exp. 2014;63:20–31.

33. Gutierrez OM, Januzzi JL, Isakova T, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009;119:2545–52.

34. Faul C, Amaral AP, Oskouei B, et al. FGF-23 induces left ventricular hypertrophy. J Clin Invest. 2011;121:4393–408.

35. Di Marco GS, Reuter S, Kentrup D, et al. Treatment of established left ventricular hypertrophy with fibroblast growth factor receptor blockade in an animal model of CKD. Nephrol Dial Transplant. 2014;29:2028–35.

36. Grabner A, Amaral AP, Schramm K, et al. Activation of cardiac fibroblast growth factor receptor 4 causes left ventricular hypertrophy. Cell Metab. 2015;22:1020–32.

37. Khan, I. A., Fink, J., Nass, C., Chen, H., Christenson, R., & defilippi, C. R. (2006). N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide for identifying coronary artery disease and left ventricular hypertrophy in ambulatory chronic kidney disease patients. The American journal of cardiology, 97(10), 1530-1534.

38. Takami Y, Horio T, Iwashima Y, Takiuchi S, Kamide K, Yoshihara F, Nakamura S, Nakahama H, Inenaga T, Kangawa K, Kawano Y. Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. Am J Kidney Dis 2004;44:420 – 428.

39. Dasgupta A, Chow L, Tso G, Nazareno L. Stability of NT-pro BNP in serum specimens collected in Becton Dickinson Vacutainer (SST) tubes. Clin Chem 2003;49:958 –960.

40. hlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005;352: 2049 –2060.

41. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis 2003;41:571–579