SERUM FGF23 CORRELATION WITH SERUM CREATININE IN ACUTE KIDNEY INJURY

Mahmoud Naguib Elsayed Elkot[1], Nagy Abdel-Hady Mohamed Sayed-Ahmed[2], Ahmed Ahmed Ahmed Al Deep[3], Mohamed Kamal Emad Eldin Salama Nassar[4], Mohamed Ali Atwa[5]

Article History: **Received:**29.04.2023 **Revised:** 28.05.2023 **Accepted:** 05.06.2023

Abstract

Background and Aims:
Serum FGF23 is known to markedly rise in patients with chronic kidney disease and has been found to be associated with dysregulated mineral metabolism and cardiovascular morbidity and mortality in these patients. It was discovered also that FGF23 rise in patients with acute kidney injury and has been suggested that its high level in those patients is associated with adverse outcomes. Many different mechanisms have been suggested for the FGF23 rise in acute kidney injury which appears to be independent of its classic regulators as serum phosphate, PTH, and vitamin D. one of these possible mechanisms is decreased renal clearance of FGF23 with impaired renal function. In this study, correlation of FGF23 with serum creatinine and other laboratory markers were studied. **Methods:** This study was a cross-sectional study carried out at Mansoura university hospital. It included patients who were admitted to the nephrology unit with acute kidney injury. Those patients were subjected to taking history and careful examination and blood samples were taken at admission for basic laboratory investigations, serum creatinine, and serum FGF23 measurement. **Results:** The study included 64 patients. Serum FGF23 in those patients showed no correlation with serum creatinine at admission. However, it showed significant positive correlation with white blood cell count and platelet count. **Conclusions:** Serum FGF23 showed no correlation with serum creatinine at admission in patients with acute kidney injury.

Keywords: FGF23; creatinine; correlation, AKI

1. Internal medicine department, Nephrology unit, Mansoura faculty of medicine, Mansoura university, Egypt.
2. Professor of Internal Medicine-Nephrology, Faculty of Medicine, Mansoura University.
3. Associate Professor of Internal Medicine-Nephrology, Faculty of Medicine, Mansoura University.
4. Associate Professor of Internal Medicine-Nephrology, Faculty of Medicine, Mansoura University.
5. Professor of Clinical Pathology, Faculty of Medicine, Mansoura University.

[*]**Corresponding author:** Mahmoud Elkot, M.Sc. **Email:** mahmoud_naguib_elkot@yahoo.com

DOI: 10.48047/ecb/2023.12.8.52

Introduction:
Acute kidney injury (AKI) is a global health problem that significantly affects morbidity and mortality [1, 2]. It is often under-recognized and is associated with severe consequences [3, 4]. Emerging evidence suggests that even a small increase in serum creatinine level is associated with worse outcomes and higher mortality in both short and long-term follow-up [5, 6]. New prognostic tests may offer an earlier diagnosis, better assessment and improved care [7].

Dysregulated mineral metabolism, including hypocalcemia, hyperparathyroidism, and low circulating levels of 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D), is an important feature of critical illness [8], and is especially pronounced among patients with acute kidney injury [9].

Fibroblast growth factor 23 (FGF23) is an osteocyte derived hormone which is initially discovered for its pathologic role in syndromes of urinary phosphate wasting [10]. FGF23 increases urinary phosphate excretion, and it inhibits the conversion of 25D to its biologically active form, 1,25D, while also stimulating the catabolism of both 25D and 1,25D [11].

Elevated FGF23 levels are now recognized as a key feature of dysregulated mineral metabolism in patients with CKD [12] and are one of the most robust and independent predictors of cardiovascular disease [13] and death [14] in this patient population. It was

found to be increased with nephropathy progression in CKD population [15-17].

The first evidence that circulating FGF23 levels are increased in human AKI came from a case report by Leaf and his colleagues [18]. Subsequent studies confirmed this initial observation including studies performed across a variety of AKI [9, 19, 20].

Classic regulators of FGF23 production, such as PTH, 1,25D, and phosphate, do not appear to play a significant role in this acute increase of FGF23 in AKI [19]. Given that the kidneys play a role in FGF23 clearance, impaired excretion, or catabolism of FGF23 by the kidneys in the setting of AKI theoretically could contribute to increased circulating levels [21, 22]

In contrast to CKD, few studies investigated FGF23 in critical illness. Higher FGF23 levels were reported to be associated with an increased risk of the composite end point of acute kidney injury or death in critically ill patients [22-24].

In this study, we investigated the correlation of FGF23 with serum creatinine and other laboratory parameters in patients with acute kidney injury.

Patients and methods:

Patients

This is a cross-sectional study of patients who were presented with acute kidney injury in the duration between May 2021 and May 2022. The study was conducted at the nephrology unit of Mansoura university hospital at Mansoura University. A total of 64 patients with acute kidney injury were enrolled in our study. Inclusion criteria were patients older than 18 years and acute kidney injury according to KDIGO definition. Exclusion criteria included patients younger than 18 years, patients with rhabdomyolysis, active malignancy, or post-renal acute kidney injury. Data included patients' baseline demographics, comorbidities, causes of acute kidney injury, and presenting symptoms.

This study protocol was reviewed and approved by the institutional review board of Mansoura faculty of Medicine (IRB). The study was conducted in accordance with the Declaration of Helsinki and the consolidated Good Clinical Practice guidelines. Informed written consent was obtained from all participants after simple explanations of the benefits, details, and possible complications of the planned procedure.

Measurements

Blood samples were obtained at admission for measurement of serum FGF23, serum creatinine, complete blood count, serum albumin, serum bicarbonate, serum calcium, and serum phosphorus.

Statistical analysis:

Categorical variables were expressed as group percentages and were compared for independent samples using Chi-square test. Continuous data were presented as medians (min-max) and were compared using Wilcoxon's signed ranks test. The statistical significance level was set at <0.05. Statistical analyses were performed using SPSS version 25.

Results:

In this study, 64 patients were included: 36 males (56.3%), and 28 females (43.8%). Their median age was 59 years. In the current study hypertension was the most common associated comorbidity in acute kidney injury patients followed by DM.

Dehydration was found to be the most common cause of acute kidney injury, being present in 50% of studied patients, followed by use of NSAID, UTI, sepsis, use of RAS inhibitors, shock, and AGN. Oliguria was the commonest presenting symptom in the studied acute kidney injury patients followed by symptoms suggestive of infection, and edema.

Table (1): Baseline characteristics.

Factor	Patient n= 64	Factor	Patient n=64
-**Age:** median (min-max)	59 (18-81)		
-Gender Males [n (%)]	36 (56.3%)	**Females [n (%)]**	28 (43.8%)
Comorbidities			
-HTN [n (%)]	34 (53.1%)	**-DM [n (%)]**	23 (35.9%)
-CLD [n (%)]	7 (10.9%)	**-CHF [n (%)]**	3 (4.7%)
-SLE [n (%)]	3 (4.7%)	**-No comorbidities [n (%)]**	21 (32.8%)
Presentation:			
-Oliguria [n (%)]	39 (60.9%)	**-Dysuria [n (%)]**	14 (26.6%)
-Haematuria [n (%)]	6 (9.4%)	**-Edema [n (%)]**	23 (35.9%)
-Infection symptoms [n (%)]	26 (40.6%)	**-Disturbed conscious [n (%)]**	8 (12.5%)
AKI causes:			
-Dehydration [n (%)]	32 (50%)	**-Sepsis [n (%)]**	21 (32.8%)
-Shock [n (%)]	8 (12.5%)	**-UTI [n (%)]**	28 (43%)
-NSAIDs [n (%)]	28 (43.8%)	**-RAS inhibitors [n (%)]**	16 (25%)

-AGN [n (%)]	6 (9.4%)	**-Contrast [n (%)]**	1 (1.6%)

WBCS and platelet counts showed positive correlation with serum FGF23. There was no significant correlation between serum FGF23, and other laboratory parameters including serum albumin, calcium, phosphorus, and bicarbonate as shown in table 2.

Table (2): FGF23 correlations.

Lab	ρ	P
Serum creatinine on admission	-0.117	0.355
Serum albumin	-0.194	0.125
Hb	0.072	0.574
Platelet count	0.377	**0.002**
WBCs	0.299	**0.017**
$HCO3^-$	-0.054	0.684
Ca	0.094	0.461
PO4	0.056	0.658

DISCUSSION:

FGF23 was initially discovered as an important regulator of calcium and phosphate metabolism. It markedly increases in patients with CKD, and is associated with cardiovascular disease [25, 26]. Later on, it was discovered also that serum FGF23 increases significantly in patients with acute kidney injury and could be a promising predictor of acute kidney injury and related adverse outcomes [20, 22].

In our study we tried to investigate the correlation between serum FGF23 and serum creatinine and other laboratory markers in patients admitted to the hospital with acute kidney injury. Our study showed that serum FGF23 did not correlate with serum creatinine measured at admission in the studied patients with acute kidney injury. In harmony with this, serum FGF-23 did not clearly correlate with serum creatinine in nephrectomized rats [27].

Serum FGF23 in this study correlated positively with white blood cell count and platelet count. In agreement with this, Takashi et al. reported significant association between serum FGF23 and WBC count. However, this association became non-significant after logistic regression analysis, yet serum FGF23 showed significant association with C-reactive protein [28]. Another study also reported positive correlation between serum FGF23 and neutrophil count [29]. In addition, platelet count was reported to correlate positively with serum FGF23 in children with iron deficiency anemia [30]. These findings may reflect the known role of higher white blood cell and platelet counts as markers of inflammation [31-34] which by its turn increases serum FGF23 [35-37].

The current study highlights the changes of serum FGF23 in AKI and that its level did not correlate with serum creatinine suggesting that impaired FGF23 clearance may not be the only mechanism of FGF23 rise in AKI.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Funding:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES:

1. Bellomo, R., J.A. Kellum, and C. Ronco, *Acute kidney injury.* The Lancet, 2012. 380(9843): p. 756-766.
2. Susantitaphong, P., et al., *World incidence of AKI: a meta-analysis.* Clinical Journal of the American Society of Nephrology, 2013. 8(9): p. 1482-1493.
3. Mehta, R.L., et al., *Spectrum of acute renal failure in the intensive care unit: the PICARD experience.* Kidney Int, 2004. 66(4): p. 1613-21.
4. Palevsky, P.M., *Epidemiology of acute renal failure: the tip of the iceberg*. 2006, Am Soc Nephrol.
5. Lassnigg, A., et al., *Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study.* J Am Soc Nephrol, 2004. 15(6): p. 1597-605.
6. Chertow, G.M., et al., *Acute kidney injury, mortality, length of stay, and costs in hospitalized patients.* J Am Soc Nephrol, 2005. 16(11): p. 3365-70.
7. Hall, P.S., et al., *The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation.* Health Technol Assess, 2018. 22(32): p. 1-274.
8. Lee, P., J.A. Eisman, and J.R. Center, *Vitamin D deficiency in critically ill patients.* N Engl J Med, 2009. 360(18): p. 1912-4.
9. Leaf, D.E., et al., *FGF-23 levels in patients with AKI and risk of adverse outcomes.* Clin J Am Soc Nephrol, 2012. 7(8): p. 1217-23.

10. Pereira, R.C., et al., *Patterns of FGF-23, DMP1, and MEPE expression in patients with chronic kidney disease.* Bone, 2009. 45(6): p. 1161-8.
11. Shimada, T., et al., *FGF□23 is a potent regulator of vitamin D metabolism and phosphate homeostasis.* Journal of Bone and Mineral Research, 2004. 19(3): p. 429-435.
12. Hasegawa, H., et al., *Direct evidence for a causative role of FGF23 in the abnormal renal phosphate handling and vitamin D metabolism in rats with early-stage chronic kidney disease.* Kidney Int, 2010. 78(10): p. 975-80.
13. Scialla, J.J., et al., *Fibroblast growth factor-23 and cardiovascular events in CKD.* J Am Soc Nephrol, 2014. 25(2): p. 349-60.
14. Isakova, T., 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): p. 2432-2439.
15. Komaba, H., *New Developments in CKD-MBD. Development and progression of CKD-MBD in predialysis period-when and how?* Clinical calcium, 2014. 24(12): p. 1771-1778.
16. Larsson, T., 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 international, 2003. 64(6): p. 2272-2279.
17. Portale, A.A., et al., *Fibroblast Growth Factor 23 and Risk of CKD Progression in Children.* Clin J Am Soc Nephrol, 2016. 11(11): p. 1989-1998.
18. Leaf, D.E., M. Wolf, and L. Stern, *Elevated FGF-23 in a patient with rhabdomyolysis-induced acute kidney injury.* Nephrol Dial Transplant, 2010. 25(4): p. 1335-7.
19. Christov, M., et al., *Plasma FGF23 levels increase rapidly after acute kidney injury.* Kidney International, 2013. 84(4): p. 776-785.
20. Shaker, A.M., et al., *Fibroblast growth factor-23 as a predictor biomarker of acute kidney injury after cardiac surgery.* Saudi J Kidney Dis Transpl, 2018. 29(3): p. 531-539.
21. Mace, M.L., et al., *Key role of the kidney in the regulation of fibroblast growth factor 23.* Kidney Int, 2015. 88(6): p. 1304-1313.
22. Leaf, D.E., et al., *Fibroblast Growth Factor 23 Levels Associate with AKI and Death in Critical Illness.* Journal of the American Society of Nephrology, 2017. 28(6): p. 1877.
23. Rygasiewicz, K., et al., *C-terminal and intact FGF23 in critical illness and their associations with acute kidney injury and in-hospital mortality.* Cytokine, 2018. 103: p. 15-19.
24. Leaf, D.E., et al., *Fibroblast growth factor 23 associates with death in critically ill patients.* Clinical Journal of the American Society of Nephrology, 2018. 13(4): p. 531-541.
25. Marthi, A., et al., *Fibroblast Growth Factor-23 and Risks of Cardiovascular and Noncardiovascular Diseases: A Meta-Analysis.* Journal of the American Society of Nephrology, 2018. 29(7): p. 2015.
26. Mitsnefes, M.M., et al., *FGF23 and Left Ventricular Hypertrophy in Children with CKD.* Clinical Journal of the American Society of Nephrology, 2018. 13(1).
27. Saito, H., et al., *Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo.* J Biol Chem, 2005. 280(4): p. 2543-9.
28. Takashi, Y., et al., *Circulating FGF23 is not associated with cardiac dysfunction, atherosclerosis, infection or inflammation in hemodialysis patients.* Journal of Bone and Mineral Metabolism, 2020. 38(1): p. 70-77.
29. Kristjansdottir, H.L., et al., *High platelet count is associated with low bone mineral density: The MrOS Sweden cohort.* Osteoporosis International, 2021. 32(5): p. 865-871.
30. Elsayed, w. and S.H. Qushwa, *Study of fibroblast growth factor-23 in iron deficiency anemia in group of Egyptian Children.* Zagazig University Medical Journal, 2022. 28(3): p. 583-593.
31. Pearson, T.A., et al., *Markers of Inflammation and Cardiovascular Disease.* Circulation, 2003. 107(3): p. 499-511.
32. Santimone, I., et al., *White blood cell count, sex and age are major determinants of heterogeneity of platelet indices in an adult general population: results from the MOLI-SANI project.* Haematologica, 2011. 96(8): p. 1180-8.
33. Franco, A.T., A. Corken, and J. Ware, *Platelets at the interface of thrombosis, inflammation, and cancer.* Blood, 2015. 126(5): p. 582-588.
34. Lee, H.S., et al., *Platelet and white blood cell count are independently associated with sarcopenia: A nationwide population-based study.* Thrombosis Research, 2019. 183: p. 36-44.
35. David, V., C. Francis, and J.L. Babitt, *Ironing out the cross talk between FGF23 and inflammation.* American Journal of Physiology-Renal Physiology, 2016. 312(1): p. F1-F8.
36. Francis, C. and V. David, *Inflammation regulates fibroblast growth factor 23 production.* Curr Opin Nephrol Hypertens, 2016. 25(4): p. 325-32.
37. Rodríguez-Ortiz, Maria E., et al., *Inflammation both increases and causes resistance to FGF23 in normal and uremic rats.* Clinical Science, 2020. 134(1): p. 15-32.