Editorial

American Journal of Nephrology

Am J Nephrol 2017;45:146–148
DOI: 10.1159/000454961

Published online: December 23, 2016

# Is Fibroblast Growth Factor 23 the New Biomarker for Cardiovascular Mortality in Chronic Kidney Disease Patients?

Guido Filler[a–c] Christopher McIntyre[a, b, d]

[a]Department of Paediatrics, [b]Department of Medicine, and [c]Department of Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, and [d]Department of Medical Biophysics, University of Western Ontario, London, ON, Canada



Individuals with chronic kidney disease (CKD) are at a high risk for cardiovascular vascular disease (CVD) mortality, and advances in this field form the final frontier of CKD research [1, 2]. There has been little progress to further our understanding of this comorbidity and to improve the outcomes of CVD-associated morbidity [3]. Patients with CKD also suffer from CVD as a result of several factors such as hypertension, volume overload, diabetes mellitus, tobacco use, physical inactivity, psychosocial stress, type of CKD, proteinuria, dysregulated renin–angiotensin–aldosterone system, dyslipidemia, malnutrition, infections, thrombogenic factors, elevated homocysteine, anemia, and CKD-inherent factors. The most prominent CKD-inherent factors appear to be uremia, renal osteodystrophy, vitamin D pathophysiology, and the direct effects of fibroblast growth factor 23 (FGF23), a small molecular weight protein, on the myocardium and the large vessels [3]. FGF23 accumulates in CKD and is a potent negative regulator of circulating phosphate and $1,25(OH)_2D_3$ concentrations [4]. It also functions as an endocrine hormone by targeting cells in the kidneys and parathyroid glands, where it binds to the Klotho coreceptor and converts FGF receptor (FGFR) 1c into a specific FGF23 receptor. FGF23 induces phosphaturia and lowers serum phosphorus by reducing the number of sodium–phosphate co-transporters in the kidney's proximal tubules [5]. It also directly suppresses renal 1α-hydroxylase, decreasing the rate at which 25-hydroxyvitamin D is converted to its active metabolite, $1,25(OH)_2D_3$ [5]. The serum concentration of FGF23 is also highly correlated with a patient's cystatin C eGFR [4]. Lastly, FGF23 may cause left ventricular hypertrophy by inducing cardiac myocyte hypertrophy through Klotho-independent pathways that are mediated by FGFR-dependent signaling in the calcineurin-nuclear factor of activated T cells (NFAT) cascade [6]. This effect may be reversible with FGF23 receptor blockers. A comprehensive meta-analysis confirming the value of using FGF23 as a biomarker for CVD-associated mortality has been elusive.

With that in mind, we were delighted to encounter such a meta-analysis by Xue et al. [7] in this edition of the *American Journal of Nephrology*. Their rigorous analysis systematically evaluated 15 prospective cohort studies comprising a large sample size of 15,355 subjects with pre-dialysis CKD stages I–V. Their publication not only summarized the clear association between FGF23 and mortality, but also demonstrated the non-linear dose-dependent relationship between FGF23 and all-cause mortality [7]. In their systematic meta-analysis, a high FGF23 level was associated with an increased risk of all-cause



E-Mail karger@karger.com
www.karger.com/ajn

Guido Filler, MD, PhD, FRCPC
Professor of Paediatrics, Medicine, and Pathology and Laboratory Medicine
Department of Paediatrics, University of Western Ontario, Children's Hospital of Western Ontario, 800 Commissioners Road East, London, ON N6A 5W9 (Canada)
E-Mail guido.filler@lhsc.on.ca

mortality (RR 1.46, 95%CI 1.38–1.55, $p < 0.001$) and CVD (RR 1.37, 95% CI 1.15–1.63, $p < 0.001$). In order to perform this analysis, the team had to compare the results from various c-terminal and intact FGF23 ELISAs by Kainos, Immutopics, and Kyowa Medex [7]. The interquartile ranges of the studies widely varied and used both arbitrary units (RU) and pg/mL. The majority used the former and had a wide range of 1.5–2,200 RU/mL. Either the low end of the reference level or the lowest level of each study was regarded as the low level in the overall analysis, while the lowest reference level of 51 RU/mL in the included studies was chosen as the low level of the dose–response analysis. A definition of high FGF23 levels had to be developed in order for the team to be able to compare the results from the various studies. When an included study compared the reference level of FGF23 with the composite higher level, the authors used the higher level as the high level. In studies that just compared the lowest level or referent category of FGF23 with the higher categories (≥2 categories), the authors used the highest category as the high level. They elegantly illustrate the non-linear increase of the C-terminal FGF23 level in RU/mL and the relative risk for CVD mortality [7]. The dose–response relationship helps to strengthen this message. Notably, most of these studies were performed in elderly cohorts and only one study included patients as young as 21 years old.

This meta-analysis has many advantages, including its thorough selection of studies, large total sample size, and exclusive selection of prospective studies. The authors also carefully controlled for known covariates, such as age, gender, ethnicity, estimated glomerular filtration rate level, smoking, and calcium phosphate metabolism; it remains to be seen whether additional covariates exist [3]. As with any meta-analysis or systematic review, this study may have been subject to a publication bias. An ideal meta-analysis would also only include studies performed in children and young adults to eliminate the possibility of Framingham-type risk factor confounders. Nonetheless, this study by Xue et al. [7] strengthens our knowledge of the emerging role of this important biomarker and highlights its importance in predicting CVD risk in patients with CKD.

So, can we now recommend performing routine FGF23 testing? The answer is no. We must first develop internationally certified reference materials and both standardize and automate FGF23 assays as a whole, rendering them less labor intensive and less expensive. Unfortunately, the bench-to-bedside process is complicated and most biomarkers never make it into clinical routine. Organizations such the National Institute for Health and Care Excellence in the National Health System of the United Kingdom and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative/Kidney Disease-Improving Global Outcomes must critically review these assays and issue recommendations. To become fully automated, FGF23 testing should be translated to multianalyzer platforms.

While measuring FGF23 is important by itself, we must also identify external factors that affect FGF23, so that we can recommend or modify behaviors and factors to help patients lower their FGF23 and thereby improve their CKD-associated CVD outcomes. Still, while the causes of CKD-associated CVD are complex and classic Framingham-type risk factors are less crucial for our CKD patients' survival, the importance of FGF23 as a predictive biomarker is becoming evident and strategies for lowering FGF23 beyond a renal transplant and a functioning graft must be systematically explored [3]. As the authors conclude, future prospective studies using a standardized FGF23 assay and employing any adjustments to account for all possible covariates are required to confirm these associations and should then form the basis for large prospective interventional studies.


## Acknowledgment

We would like to thank Marta Kobrzynski, Research Assistant to Dr. Filler, for her work on editing the manuscript.


## Disclosure Statement

The authors have no conflicts of interest to declare.

## References


1 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305.

2 Collins AJ, Foley R, Herzog C, Chavers B, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Zhang R, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L: Excerpts from the United States Renal Data System 2007 annual data report. Am J Kidney Dis 2008;51(1 suppl 1):S1–S320.

3 Freundlich M, Lipshultz SE, Filler G: Chronic kidney disease and cardiac morbidity – what are the possible links? Prog Pediatr Cardiol 2016;41:89–95.
4 Filler G, Liu D, Huang SH, Casier S, Chau LA, Madrenas J: Impaired GFR is the most important determinant for FGF-23 increase in chronic kidney disease. Clin Biochem 2011; 44:435–437.
5 Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T: Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest 2004;113:561–568.
6 Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M: FGF23 induces left ventricular hypertrophy. J Clin Invest 2011;121:4393–4408.
7 Xue C, Yang B, Zhou C, Dai B, Liu Y, Mao Z, Yu S, Mei C: Fibroblast growth factor 23 predicts all-cause mortality in a dose-response fashion in pre-dialysis patients with chronic kidney disease. Am J Nephrol 2017; 45:149–159.