Elevated Fibroblast Growth Factor 23 Levels Are Associated With Greater Diastolic Dysfunction in ESRD

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ife expectancy in individuals with chronic kidney disease (CKD) is unacceptably low, and cardiovascular disease remains the leading cause of death. Above and beyond established cardiovascular disease risk factors that are highly prevalent in CKD patients, unique risk factors such as abnormal mineral metabolism are widely hypothesized to contribute to the pathogenesis of cardiovascular disease in CKD.

Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone produced mainly by osteocytes. As kidney function declines in CKD, FGF23 rises early and counteracts phosphate accumulation. Elevated FGF23 levels are independently associated with increased risk of cardiovascular disease and mortality in different populations, including among those with CKD. In animal models and in vitro, FGF23 has a direct pathogenic effect, causing left ventricular (LV) hypertrophy by activating fibroblast growth factor receptor 4 on cardiac myocytes. In prior human observational studies, higher FGF23 has been associated with arrhythmias, and decreased LV systolic function. Given animal data suggesting that FGF23 may induce LV hypertrophy, and human data demonstrating associations of elevated FGF23 with LV hypertrophy—one potential pathologic driver of diastolic dysfunction—we hypothesized that higher FGF23 levels may be associated with diastolic dysfunction, a common complication of CKD.

**METHODS**

Please see Supplementary Material.

**RESULTS**

Baseline characteristics of the study cohort are shown in Table 1, stratified by quartiles of intact (i) FGF23. Seventy percent of the 47 participants were men, and 62% had preserved LV ejection fraction (EF). The mean (±SD) age was 61 (±20) years, mean phosphate was 5.0 (±1.4) mg/dl; mean LVEF was 51 (±13) %, mean left atrial volume was 58 (±27) ml, mean tricuspid velocity was 2.6 (±0.5) m/sec, and the mean E (transmitral early filling velocity)/A (transmitral late filling velocity) ratio was 1.4 (±0.5). A total of 94% (44 of 47) of patients had LV diastolic dysfunction, and 53% (25 of 47) had LV hypertrophy (LVH).

Median iFGF23 was elevated at 1135 (interquartile range: 361, 3195) pg/ml, which is comparable to values observed in end-stage kidney disease cohorts. The strongest association was between higher levels of iFGF23 and grades of diastolic dysfunction (r_s = 0.75; P < 0.001), followed by serum phosphate and iFGF23 (r_s = 0.51; P < 0.001). In the univariate model, elevated levels of natural log–transformed iFGF23 were significantly associated with a higher grade of LV diastolic dysfunction (R^2 = 0.51; 95% confidence interval for slope, 1.7–3.4; P < 0.001). In a multivariate model, this relationship remained significant and was essentially unaltered after adjusting for age, phosphate, and LVEF (R^2 = 0.5; 95% confidence interval for slope, 1.01–1.5; P < 0.001; Figure 1).

**DISCUSSION**

In this study of 47 patients with end-stage kidney disease treated with hemodialysis, we found that higher levels of iFGF23 were associated with LV diastolic dysfunction. The association appeared to have a step-wise linear relationship with grades of severity of diastolic dysfunction, independently of LVEF. Although observational data reported here cannot prove causality, these data parallel observations made...
In contrast, in a nondialysis CKD patients where high FGF23 and low Klotho levels were strongly and longitudinally associated with a higher grade of left ventricular diastolic dysfunction ($R^2 = 0.51$; 95% confidence interval for slope, 1.7–3.4; $P < 0.001$).

**Figure 1.** Box plots showing the relationship between the grading of diastolic dysfunction and the natural logarithm of intact fibroblast growth factor 23 (FGF23) in 47 hemodialysis patients. Elevated levels of natural log-transformed intact FGF23 were significantly associated with a higher grade of left ventricular diastolic dysfunction ($R^2 = 0.51$; 95% confidence interval for slope, 1.7–3.4; $P < 0.001$).

In conclusion, this study is the first to our knowledge to report an association between higher iFGF23 levels and severity of LV diastolic dysfunction in end-stage renal disease patients receiving hemodialysis. FGF23 has multiple adverse effects on the cardiovascular system, and understanding of the complex interplay of these effects in CKD patients is evolving. Future larger studies examining the relationship between FGF23 and the progression of diastolic dysfunction are warranted in patients with CKD, and ultimately, studies that target FGF23 lowering should be conducted to evaluate the effects on cardiac function.

**DISCLOSURE**

All the authors declared no competing interests.

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**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.
Molecular Genetic Diagnosis of Omani Patients With Inherited Cystic Kidney Disease

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Chronic kidney disease (CKD) is defined as abnormalities in the structure or function of the kidney that are present for more than 3 months and have implications for health. Inherited kidney diseases are a major cause of CKD and often lead to progressive CKD resulting in end-stage renal disease (ESRD). Cystic kidney diseases are common inherited causes of ESRD in both children and adults, accounting for 6%–12% of cases.1,2

Inherited forms of cystic kidney have been associated with dysfunction of the primary cilia.3 These diseases are often termed renal ciliopathies and are part of a growing number of inherited diseases that include autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD),4 tuberous sclerosis complex (TSC),5 autosomal dominant tubulointerstitial kidney disease (ADTKD),6 nephronophthisis-related ciliopathies (NPHP-RC),7 Bardet-Biedl syndrome, Senior-Löken syndrome, Meckel Gruber syndrome, Joubert syndrome, and others.8

ADPKD is the most common autosomal dominant inherited ciliopathy, accounting for 10% of all patients with ESRD requiring renal replacement therapy.9 It is characterized by bilateral renal cysts, leading to enlarged kidneys and kidney failure. Extrarenal manifestations such as liver cysts, intracranial aneurysms, and mitral valve prolapse are also frequently noted. Most cases of ADPKD are caused by mutations in PKD1 (85%) and PKD2 (15%), although recently mutations in GANAB,9 and DNAJB11 have been associated with similar phenotypes in genetically unresolved