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Serum Fibroblast Growth Factor 21 Is Associated With Renal Function and Chronic Kidney Disease in Community-Dwelling Adults

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To the editor

Fibroblast growth factor 21 (FGF21) is a recently discovered hormone that is expressed primarily in the liver and stimulates glucose uptake in adipocytes.¹ Circulating FGF21 is elevated in adults with obesity,² metabolic syndrome,² diabetes mellitus,³ and coronary heart disease.⁴ In a cohort in Hong Kong, elevated FGF21 predicted incident diabetes mellitus.⁵ FGF21 levels are elevated in end-stage renal disease.⁶ The relationship of FGF21 with renal function and chronic kidney disease (CKD) has not been well characterized in community-dwelling adults. We hypothesized that serum FGF21 was independently associated with renal function and CKD.

We characterized serum FGF21 and renal function in 744 adults in the Baltimore Longitudinal Study of Aging (BLSA)⁷ who were seen between 2002 and 2007. The BLSA has continuing approval from the Institutional Review Board (IRB) of the MedStar Research Institute. The protocol for the present study was approved by the IRB of the Johns Hopkins School of Medicine. Fasting blood samples were collected at 7–8 AM and stored at –80°C until the time of analysis. Serum creatinine was measured using the Jaffe method. Serum FGF21 was measured using ELISA (Quantikine Human FGF-21 ELISA, R & D Systems, Minneapolis, MN)¹⁴ with intra-assay and inter-assay coefficients of variability of 2.8% and 7.0%. CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration equation.⁸ Multivariable logistic and linear regression models were used to examine the relationship of log serum FGF21 and other factors with CKD and eGFR, respectively. Covariates included in the multivariable models were basic demographic variables (age, gender, race) and variables that were significantly associated with tertiles of serum FGF21. Diabetes was included in the

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Candace Crasto: Laboratory analysis, preparation of manuscript.

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Luigi Ferrucci: Collection of patient data, data analysis and interpretation, preparation of manuscript.

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multivariate models because it is known to be associated with higher FGF21 levels and abnormal glucose metabolism.

Overall, the median (25th, 75th percentile) serum FGF21 concentration was 227 (127, 371) pg/mL. Of the 744 adults, 144 (19.3%) had CKD. The characteristics of the participants by tertile of serum FGF21 are shown (Table). Age, gender, race, current smoking, body mass index (BMI), eGFR, and proportion of individuals with hypertension, angina, congestive heart failure, and CKD were significantly different across tertiles of FGF21. There were no significant differences in diabetes, myocardial infarction, stroke, and cancer by tertiles of serum FGF21.

Log FGF21 (per 1 SD increase [0.77]) was associated with CKD in a multivariable logistic regression model adjusting for age, race, sex, smoking, BMI, and chronic diseases (hypertension, congestive heart failure, angina, and diabetes) (OR 1.32, 95% CI 1.03, 1.69, $P = 0.03$). Results were similar if diabetes was excluded from the model (OR 1.33, 95% CI 1.04, 1.70, $P = 0.02$). Log FGF21 (per 1 SD increase) was associated with eGFR in a multivariable linear regression model adjusting for age, race, sex, smoking, BMI, and chronic diseases (hypertension, congestive heart failure, angina, and diabetes) ($\beta = -1.47$, SE = 0.59, $P = 0.01$). Results were similar if diabetes was excluded from the model ($\beta = -1.48$, 95% SE = 0.59, $P = 0.01$).

The present study shows that serum FGF21 levels are independently associated with renal function and CKD in community-dwelling adults. These findings are consistent with two previous studies which suggested that circulating FGF21 concentrations were associated with renal function in diabetics,⁵ and in a mixed population of healthy controls and patients on hemodialysis or with CKD.⁶ In the present study, the relationship of serum FGF21 with renal function and CKD was consistent even after exclusion of participant with diabetes.

Serum FGF21 concentrations may be increased in individuals with reduced renal function because of the inability of the kidney to clear FGF21 in the urine. An alternative explanation may be that elevated FGF21 is causally related to reduced renal function, but currently there is little evidence to support such a hypothesis. In any case, the findings from the present study highlight the potential importance of adjusting for renal function in future epidemiological studies of circulating FGF21.

The strengths of this study include the relatively large sample size of community-dwelling adults and the rigorously timed and standardized collection of fasting serum samples, as FGF21 levels have been shown to have a circadian rhythm.⁹ A limitation of the study is the cross-sectional design, as the direction of the association between elevated circulating FGF21 and renal function is unknown. Further studies are needed to determine whether high levels of circulating FGF21 precede compromised renal function, or serve as a biomarker that is retained as renal function declines.

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Table

Characteristics of 744 adults by tertiles of serum FGF21 in the Baltimore Longitudinal Study of Aging

Characteristic *	Tertile of Serum FGF21			<i>p</i> [†]
	≤ 163 pg/mL (n = 248)	163–305 pg/mL (n = 248)	> 305 pg/mL (n = 248)	
Age, y	57.5 (50.2, 66.7)	65.1 (56.8, 75.2)	71.2 (61.3, 77.9)	<0.0001
Male gender, %	44.3	56.0	49.2	0.03
Race, white, %	58.5	63.3	75.4	0.0002
Current smoking, %	2.0	4.4	7.3	0.02
Body mass index, kg/m ²	25.7 (23.2, 29.4)	26.6 (24.0, 30.4)	26.8 (24.4, 30.8)	0.01
Estimated glomerular filtration rate, mL/(min·1.73m ²)	81.4 (70.9, 93.2)	76.3 (64.8, 89.7)	71.0 (57.1, 82.9)	<0.0001
Chronic kidney disease, %	9.3	18.9	29.8	<0.0001
Hypertension, %	23.8	31.5	39.5	0.0008
Diabetes, %	4.4	6.1	7.3	0.4
Angina, %	8.1	10.5	14.9	0.05
Myocardial infarction, %	2.8	2.8	6.1	0.10
Stroke, %	0.4	0	0.8	0.4
Heart failure, %	0	0	2.0	0.007
Cancer, %	8.1	12.1	12.1	0.2

* Values are median (25th, 75th percentile) for continuous variables, and % for categorical variables.

[†] Kruskal Wallis test used for continuous variables, chi-square test used for categorical variables.