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Original Investigation

Fibroblast Growth Factor 23 and Sudden Versus Non-sudden Cardiac Death: The Cardiovascular Health Study

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Background: Elevated fibroblast growth factor 23 (FGF-23) concentrations are associated with greater risk of cardiovascular events and mortality, especially among people with chronic kidney disease (CKD). Because individuals with CKD are at an increased risk of sudden cardiac death (SCD), we sought to understand whether FGF-23 level is a stronger risk factor for SCD versus non-SCD.

Study Design: Cohort study.

Setting & Participants: 3,244 participants 65 years or older in the community-based Cardiovascular Health Study.

Predictor: Plasma FGF-23 concentrations.

Outcomes: We assessed SCD and non-SCD in these analyses. SCD was adjudicated rigorously and was defined as a sudden pulseless condition of cardiac origin in a previously stable person occurring out of hospital or in the emergency department.

Measurements: We estimated associations of baseline FGF-23 concentrations with SCD and non-SCD using Cox proportional hazards models after adjustment for demographics, cardiovascular risk factors, comorbid conditions, and kidney function. We also tested whether associations differed by CKD status.

Results: During a median follow-up of 8.1 years, there were 118 adjudicated SCD and 570 non-SCD events. After multivariable adjustment for demographics, cardiovascular risk factors, comorbid conditions, and parameters of kidney function, higher FGF-23 concentrations were an independent risk factor for non-SCD (HR [per doubling], 1.17; 95% CI, 1.06-1.30). However, elevated FGF-23 concentrations were not associated independently with SCD (HR [per doubling], 1.07; 95% CI, 0.85-1.35). In stratified analysis by CKD status (36.5% of cohort), doubling of FGF-23 concentrations was associated independently with non-SCD (adjusted HR, 1.26; 95% CI, 1.10-1.45). A similar magnitude of association was observed between FGF-23 level and SCD in the CKD subgroup; however, it was not significant (HR, 1.20; 95% CI, 0.89-1.62).

Limitations: Limited power to detect moderate-sized effects between FGF-23 level and SCD in both the primary and stratified analyses.

Conclusions: In this population-based study, FGF-23 level elevations were associated independently with non-SCD. Among individuals with CKD, the associations between FGF-23 level and SCD and non-SCD were similar.
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INDEX WORDS: Fibroblast growth factor 23 (FGF-23); chronic kidney disease (CKD); sudden cardiac death (SCD); non-SCD; cardiovascular event; cardiovascular mortality; fatal arrhythmic event; renal function; Cardiovascular Health Study (CHS); cohort study.

Fibroblast growth factor 23 (FGF-23) is a hormone that is produced in osteocytes and regulates phosphorus and 1,25-dihydroxyvitamin D (1,25$[OH]_2$D) metabolism. In the kidney, it induces renal phosphorus excretion and inhibits conversion of 25-hydroxyvitamin D to the active hormone 1,25$(OH)_2$D.[1] Elevations in

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FGF-23 concentrations are believed to occur as a physiologic response to maintain normal serum phosphorus levels. As a result, FGF-23 concentrations increase progressively in kidney disease as the capacity for phosphorus excretion declines.[2] These compensatory changes maintain normal serum phosphorus levels by inducing its excretion and suppressing $1,25(OH)_2D$ synthesis. Despite this physiologic response, clinical studies have demonstrated that higher FGF-23 concentrations are associated strongly and independently with all-cause and cardiovascular mortality, especially among individuals with chronic kidney disease (CKD).[3-7]

Because individuals with CKD are at an increased risk of arrhythmic complications and sudden cardiac death (SCD),[8,9] we sought to understand whether FGF-23 level is a stronger risk factor for SCD versus non-SCD. In experimental models, FGF-23 induces left ventricular hypertrophy (LVH), and it is an independent predictor of congestive heart failure (CHF).[3,7,10,11] Because LVH and CHF are well-known predictors of SCD and have been included in arrhythmic risk-stratification algorithms,[12] we hypothesize that FGF-23 level is an independent risk factor for SCD. Identifying unique risk factors for SCD is fundamental for the design of targeted preventive and treatment strategies. We evaluated serum FGF-23 concentration as a novel risk marker of adjudicated SCD and non-SCD events in a community-based cohort of the elderly.

METHODS

Study Population

The CHS (Cardiovascular Health Study)[13] is a community-based study of cardiovascular disease risk in ambulatory older adults initiated by the National Heart, Lung and Blood Institute (NHLBI). The CHS recruited individuals from Medicare eligibility lists in Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA. To be eligible, persons had to be 65 years or older, not institutionalized, expected to remain in the current community for at least 3 years, not under active treatment for cancer, and able to provide written informed consent. The initial 5,201 participants were enrolled from January 1989 through June 1990; an additional 687 predominantly black participants were recruited in 1992 to 1993. In-person examinations were performed annually through 1998 to 1999 and again in 2005 to 2006. Telephone interviews were conducted semiannually from 1989 to 1999 and biannually thereafter. We measured FGF-23 at the 1996 to 1997 study visit because it was the first visit at which urine albumin-creatinine ratios (ACRs) were measured. Of 3,406 individuals who participated in the 1996 to 1997 visit, we excluded those with insufficient blood specimens for FGF-23 measurement (n = 69) and those missing creatinine (n = 1) or ACR (n = 92) readings, resulting in a final analytic sample of 3,244 participants for this analysis. The institutional review boards at all relevant sites provided approval for this protocol. Finally, this protocol was implemented according to the Declaration of Helsinki.

Information for baseline confounders was obtained at the 1996 to 1997 study visit concurrent with FGF-23 measurements and included age, sex, race, self-reported health status, and cardiovascular disease risk factors, including hypertension (systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or use of antihypertensive medications), diabetes (fasting glucose $\geq$ 126 mg/dL or use of antiglycemic medications or insulin), smoking (current, former, or never), body mass index, total cholesterol level, and use of lipid-lowering medications. A 12-lead electrocardiogram also was obtained. Cystatin C was measured using a BNII nephelometer (Siemens).[14] Based on the recently published guideline from KDIGO (Kidney Disease: Improving Global Outcomes), we defined CKD using either a cystatin C–based estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2 or albuminuria (ACR $\geq$ 30 mg/g).[15]

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Fasting (8-hour) EDTA specimens collected at the 1996 to 1997 study visit were stored at −70°C until 2010, when they were thawed and measured for FGF-23 using a carboxy-terminal enzyme-linked immunosorbent assay kit (Immutopics).[3,16] Our estimates of intra- and interassay coefficients of variation ranged from 7.4% to 10.6%.

Outcomes: SCD and Non-SCD

SCD was defined as a sudden pulseless condition of cardiac origin in a previously stable person occurring out of the hospital or in the emergency department. For unwitnessed deaths, participants must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest. These definitions concur with those proposed by the NHLBI working group on SCD.[17] These cases could not have life-threatening noncardiac comorbid conditions or be under hospice or nursing home care. A non-SCD event was defined as any cardiovascular death that was not adjudicated as an SCD event.

The adjudication process was composed of multiple steps. A specialized committee in CHS adjudicated the cause of death. All out-of-hospital cardiac deaths then were reviewed to identify whether the event was an SCD or non-SCD. Comprehensive data were gathered for cardiovascular deaths from hospital records, physician interviews, next of kin and/or witnesses, death certificates, and autopsy reports when available. Survivors or successfully resuscitated events were not included in the definition of SCD. A second physician conducted a blind review of a sample of 70 potential cases with 88% inter-reviewer agreement and κ value of 0.74 for SCD.[18]

Statistical Methods

We compared baseline characteristics of participants across FGF-23 quartiles using either χ^2 or analysis of variance test. We estimated the associations between FGF-23 levels and both SCD and non-SCD using Cox proportional hazards regression models. We evaluated FGF-23 level as a continuous predictor variable to maximize statistical power. Given its right-skewed distribution, FGF-23 levels were $\log_2$ transformed, which facilitated interpretation of hazard ratios (HRs) "per doubling" of FGF-23 concentrations. In companion analyses, we assessed associations by FGF-23 quartiles, allowing the lowest quartile to serve as the reference category. In both cases, an initial model adjusted for age, sex, and race. A second model added cardiovascular risk factors, comorbid conditions (diabetes, hypertension, smoking, heart failure, and myocardial infarction), and alcohol use. A final model added eGFR and ACR. For each of the 2 outcomes, we also stratified patients by CKD status and evaluated an FGF-23 × CKD interaction term in the final adjusted model for both the SCD and non-SCD outcomes.

Analyses evaluating associations between FGF-23 level and SCD were repeated using a competing-risk framework. In particular, because the Cox proportional hazards model treats non-sudden causes of death simply as indications to censor under an