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Association of Fibroblast Growth Factor-23 Levels and Angiotensin-Converting Enzyme Inhibition in Chronic Systolic Heart Failure

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the association of fibroblast growth factor (FGF)-23 with clinical and laboratory findings, the prognostic value of FGF-23, and the relationship between angiotensin-converting enzyme inhibitor (ACEi) therapy, FGF-23 levels, and outcomes in patients with chronic systolic heart failure (HF).

BACKGROUND FGF-23 is a bone-derived hormone regulating mineral metabolism. Higher FGF-23 levels are associated with an increased risk of cardiovascular mortality or HF development. Mechanisms leading to increased FGF-23 and its prognostic value have not been thoroughly studied in HF.

METHODS FGF-23 was measured in 369 patients (mean age 59 ± 11 years, 84% male) with systolic HF. Patients were followed for adverse events (e.g., death, urgent heart transplantation, ventricular assist device implantation).

RESULTS Tricuspid regurgitation severity, chronic kidney disease (CKD), alkaline phosphatase concentrations, inferior vena cava dilation, and absence of ACEi therapy were independently associated with FGF-23. FGF-23 was independently associated with outcomes in patients without CKD (hazard ratio [HR]: 1.43, 95% confidence interval [CI]: 1.14 to 1.78), but not in CKD patients (HR: 1.12, 95% CI: 0.87 to 1.45). In patients without CKD and with FGF-23 in the highest tertile, ACEi therapy was associated with a lower risk of adverse events (HR: 0.42, 95% CI: 0.21 to 0.81), whereas no association was seen in the remaining patients (HR: 1.18, 95% CI: 0.52 to 2.70).

CONCLUSIONS In systolic HF, elevated FGF-23 is an independent predictor of adverse events, particularly in patients with preserved renal function. The association of FGF-23 with adverse events likely reflects early alterations of renal hemodynamics and renin-angiotensin system activation. Increased FGF-23 may identify a subset of HF patients benefiting from ACEi therapy. (J Am Coll Cardiol HF 2015;3:829–39) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACEi = angiotensin-converting enzyme inhibitor

BNP = B-type natriuretic peptide

CI = confidence interval

CKD = chronic kidney disease

EF = ejection fraction

eGFR = estimated glomerular filtration rate

FGF = fibroblast growth factor

HF = heart failure

HR = hazard ratio

IQR = interquartile range

RU = relative unit

RVD = right ventricular dysfunction

Sm = tissue systolic velocity

TAPSE = tricuspid annular plane systolic excursion

Fibroblast growth factor (FGF)-23 is a bone-derived hormone that primarily regulates renal phosphate handling and vitamin D metabolism (1). Several clinical and experimental studies suggested that higher FGF-23 concentrations are associated with cardiac dysfunction (2), left ventricular hypertrophy (3,4), and poor prognosis (5-7), particularly in patients with chronic kidney disease (CKD) (4,6). In the general population and in patients with stable ischemic heart disease, elevated FGF-23 increases the risk of heart failure (HF) development (8,9). However, only limited data are available on factors associated with FGF-23 level and its prognostic value among the patients with established HF (2,10). An increase in FGF-23 may reflect renal dysfunction, altered hemodynamics, or concomitant bone disease that is also common in patients with established HF (11).

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The biological activity of FGF-23 is mediated by its binding to the canonical fibroblast growth factor receptor and its coreceptor protein Klotho. The Klotho protein exists in a membrane-bound and a soluble form. Soluble Klotho is derived from the extracellular part of membrane-bound Klotho. Whereas membrane-bound Klotho is a coreceptor for FGF-23 and is vital for its phosphaturic effect (12), soluble Klotho was implicated in vascular stiffness (13) and premature aging (14). Renin-angiotensin-aldosterone system activation reduces Klotho expression, which results in a compensatory FGF-23 increase (15). Whereas some authors have suggested that the effect of FGF-23 on the cardiovascular system is Klotho dependent (16) or that increased FGF-23 is just a measure of primary loss of Klotho function (17), others showed that the pathway is independent of Klotho (3,18).

Because FGF-23 increases in the earliest stages of renal impairment (3), even before creatinine and blood urea nitrogen (19), it was suggested to be an early marker of renal injury. In previous studies in patients with stable ischemic heart disease, FGF-23 (9) and other markers of renal dysfunction (20,21) identified patients who derived greater benefit from angiotensin-converting enzyme inhibitor (ACEi) therapy. Whether ACEi therapy in patients with HF and increased FGF-23 is associated with greater clinical benefit has never been tested.

The aims of the present study were to: 1) assess the factors associated with FGF-23 level; 2) assess the prognostic value of FGF-23; 3) determine whether the association between FGF-23 and outcome may be mediated through Klotho; and 4) test the interaction between ACEi therapy, FGF-23 levels, and outcomes among patients with HF.

METHODS

PATIENTS. Criteria for patient enrollment were described previously (22). In brief, the study enrolled patients with chronic (>6 months) moderate to advanced systolic HF (ejection fraction [EF] <50%) electively hospitalized at the Institute for Clinical and Experimental Medicine between November 1, 2007 and August 31, 2011 for consideration of advanced therapies (ventricular assist device implantation, cardiac transplantation, and implantable cardioverter-defibrillator or biventricular pacemaker implantation). Patients with acute HF decompensation, hemodynamic instability, reversible cardiac dysfunction (e.g., planned valve surgery or revascularization, tachycardia-induced cardiomyopathy), need for renal replacement therapy, active malignancy, or chronic infection were excluded. Medications at the time of enrollment were recorded. Definition of a low ACEi dose for different ACEi therapy used in this study is provided in Online Table 1. The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine. Informed consent was obtained from all patients.

LABORATORY ANALYSES. Morning fasting blood samples were collected in ethylenediamine tetraacetic acid-anticoagulated and serum separator tubes and centrifuged. Serum and plasma aliquots were stored frozen at −80°C. Plasma samples were shipped to Boston, Massachusetts, on dry ice for FGF-23 and Klotho testing. FGF-23 levels were measured using the C-terminal human enzyme-linked immunosorbent assay (Immutopics, San Clemente, California). The interassay coefficients of variation were 11.8% at 29.3 relative units (RU)/ml and 5.6% at 285 RU/ml. Klotho concentrations were determined using the α-Klotho (soluble) solid-phase sandwich enzyme-linked immunosorbent assay (IBL America, Minneapolis, Minnesota). The interassay coefficients of variation were 8.0% at 773 pg/ml and 7.4% at 1,582 pg/ml.

All other biochemical analyses were performed in the Clinical Biochemistry Laboratory at the Institute for Clinical and Experimental Medicine. Plasma sodium, hepatic enzymes, glucose, and creatinine were measured in serum using the Architect