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Fibroblast growth factor 23 is related to profiles indicating volume overload, poor therapy optimization and prognosis in patients with new-onset and worsening heart failure

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ABSTRACT

Background: Fibroblast growth factor (FGF) 23 is a hormone that increases urinary phosphate excretion and regulates renal sodium reabsorption and plasma volume. We studied the role of plasma FGF23 in therapy optimization and outcomes in patients with new-onset and worsening heart failure (HF).
Methods: We measured plasma C-terminal FGF23 levels at baseline in 2399 of the 2516 patients included in the BIOlogy Study to Tailored Treatment in Chronic HF (BIOSTAT-CHF) trial. The association between FGF23 and outcome was evaluated by Cox regression analysis adjusted for potential confounders.
Results: Median FGF23 was 218.0 [IQR: 117.1–579.3] RU/ml; patients with higher FGF23 levels had a worse NYHA class, more signs of congestion, and were less likely to use an ACE-inhibitor (ACEi) or angiotensin receptor blocker (ARBs) at baseline (all $P < 0.01$). Higher FGF23 levels were independently associated with higher BNP, lower eGFR, the presence of oedema and atrial fibrillation (all $P < 0.001$). In addition, higher FGF23 was independently associated with impaired uptitration of ACEi/ARBs after 3 months, but not of beta-blockers. In multivariable Cox regression analysis, FGF23 was independently associated with all-cause mortality (hazard ratio: 1.17 (1.09–1.26) per log increase, $P < 0.001$), and the combined endpoint of all-cause mortality and HF hospitalization (1.15 (1.08–1.22) per log increase, $P < 0.001$).
Conclusions: In patients with new-onset and worsening HF, higher plasma FGF23 levels were independently associated with volume overload, less successful uptitration of ACEi/ARBs and an increased risk of all-cause mortality and HF hospitalization.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, Brain Natriuretic Peptide; BIOSTAT-CHF, BIOlogy Study to Tailored Treatment in Chronic Heart Failure; CKD, chronic kidney disease; eGFR, estimated Glomerular Filtration Rate; FGF23, fibroblast growth factor 23; HF, heart failure; JVP, jugular venous pressure; NT-pro BNP, N terminal pro Brain Natriuretic Peptide; RAAS, Renin Angiotensin Aldosterone System.

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1. Introduction

The phosphaturic hormone fibroblast growth factor 23 (FGF23) is a key regulator of phosphate metabolism by inhibiting proximal tubular phosphate reabsorption in the kidney and suppressing the generation of $1,25(OH)_2$ vitamin D [1]. In patients with chronic kidney disease (CKD), higher FGF23 levels have been consistently associated with an increased risk of cardiovascular morbidity and mortality [2,3]. FGF23 seems particularly strongly linked with heart failure [4], supported by mechanistic studies indicating that FGF23 contributes to the development of left ventricular hypertrophy (25), regulates renal sodium reabsorption and plasma volume and interacts with renin-angiotensin-aldosterone system (RAAS) activation [5–7]. Furthermore, high FGF23 levels were associated with an impaired response to sodium restriction and ACE-inhibition in CKD patients [8].

Recently, elevated levels of FGF23 have been associated with cardiovascular mortality and incident heart failure in patients with stable ischemic heart disease [9]. In chronic heart failure, it has been suggested that FGF23 is associated with disease severity and adverse outcome [10–13]. Data on FGF23 in worsening or acute heart failure are scarce, even though it has been suggested that FGF23 has a direct effect on sodium homeostasis and volume handling. The present study is the first to address the relation between FGF23, congestion, and clinical outcomes in new onset or worsening heart failure. FGF23 contributes to RAAS activation and angiotensin converting enzyme inhibitor (ACEi) therapy has been shown to be less effective in CKD patients with high FGF23 levels [7,8]. As such, or as a consequence of the suspected association with congestion and more severe heart failure, FGF23 might have an effect on the ability to receive ACEi/angiotensin receptor blocker (ARB) therapy, a first line therapy in patients with heart failure. Therefore we additionally studied whether FGF23 is associated with impaired uptitration of ACEi/ARB. Based on the above, we hypothesized that a higher plasma FGF23 level in patients with acute or worsening heart failure is associated with less successful uptitration of guideline-recommended ACEi/ARB therapy and adverse clinical outcomes.

2. Methods

2.1. Patient population

The study design of the systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) has been published previously [14,15]. In brief, the BIOSTAT-CHF trial is a large European, multicentre, multinational, prospective, observational study in which 2516 patients with new onset or worsening heart failure with either an ejection fraction of ≤40% or plasma concentrations of Brain Natriuretic Peptide (BNP) >400 pg/ml and/or N terminal pro Brain Natriuretic Peptide (NT-proBNP) >2000 pg/ml, and treated with furosemide ≥40 mg/day or equivalent, who were on ≤50% of the target dose of ACEi or ARB and beta-blocker therapy were enrolled. The trial was approved by the local ethics committee at each participating centre and complies with the declaration of Helsinki. All patients provided written informed consent.

2.2. Study design

Both inpatients and outpatients were enrolled, and had a visit at baseline and after 9 months of follow-up. During the first 3 months, the treating physician was encouraged to uptitrate ACEi/ARBs and beta-blockers to the target doses presented in the ESC heart failure guidelines [16,17]. Subsequently, patients were contacted every 6 months by telephone. At 9 months, reasons for not reaching the target dose were recorded. These unfortunately were most commonly described as "other" reason making this too unspecific for further analyses. Median follow-up was 21 months.

The endpoints selected for these analyses were all-cause mortality, and the combined endpoint of all-cause mortality or first occurrence of HF hospitalization. HF hospitalization was defined as hospitalization lasting longer than one day for which the primary reason was worsening of signs or symptoms of HF, requiring intravenous medications or an increased dose of oral diuretics.

2.3. Laboratory measurements

From 2516 enrolled patients, plasma FGF23 was determined in 2399 (95.3%) available baseline plasma samples using a human C-terminal FGF23 ELISA (Immutopics, Inc., San Clemente, CA, USA). For the missing 117 patients (4.7%) no baseline plasma samples were available. More details on this specific assay, such as inter-/intra-assay variation have been described previously [18]. Using this assay, in a cohort of 3107 community-living persons ≥65 years of age median FGF23 was 70 [51–100] RU/mL [19]. Phosphate, calcium and albumin were measured in stored samples using routine laboratory procedures. Renin and aldosterone were both measured using a RadioImmunoAssay (Renin: CisBio International; Aldosterone: IBL International) in plasma samples that had previously undergone one freeze/thaw cycle. NT-proBNP was measured using Proseek Multiplex (Olink Biosciences AB, Uppsala, Sweden). Estimated Glomerular Filtration Rate (eGFR) was calculated using the CKD-EPI eGFR formula [20].

2.4. Statistical analysis

Data with a normal distribution are presented as mean ± standard deviation, and as frequencies and percentages for categorical values. Data with a skewed distribution are presented as median with interquartile ranges. Differences between quintiles of FGF23 were tested for significance with ANOVA (normal distribution), Kruskal-Wallis (skewed distribution), and Fisher's exact test (categorical variables). A linear trend was statistically tested over quintiles of FGF23, after checking for non-linear trends. Uni- and multivariable linear regression analysis was performed with log transformed (using natural logarithm) FGF23 as a dependent variable. Transformations were checked using multifractional polynomials. Multivariable linear regression analysis, including all variables with $P < 0.10$ in univariable analysis were constructed via backward elimination and validated using bootstrap re-sampling with 1000 replicates. The model was tested for collinearity and checked by plotting residuals. Cox proportional hazard regression analysis was performed to examine associations with clinical outcomes. FGF23 was investigated as a continuous variable, and by quintiles. Multivariable models were adjusted for an outcome model specifically developed and validated in the BIOSTAT index and validation cohort with addition of markers that have previously been associated with FGF23 levels (renin, aldosterone, phosphate, albumin, calcium and eGFR, if not already included in the model) [21]. The following variables were included in the BIOSTAT risk model for all-cause mortality: age, urea, NT-proBNP, haemoglobin, and use of beta-blocker at baseline [21]. The BIOSTAT risk model for HF hospitalization includes age, previous HF hospitalization, peripheral oedema, systolic blood pressure, and eGFR [21]. Finally, the risk model for the combined endpoint includes age, previous HF hospitalization, peripheral oedema, systolic blood pressure, NT-proBNP, haemoglobin, HDL, sodium, and use of beta-blocker at baseline [21]. Interaction analyses were used to test significant interactions in subgroups that may affect the association between FGF23 and outcome. These were visualized using forest plots. Logistic regression was used to investigate the association between FGF23 and ACEi/ARB use, and whether target dose was reached. For outcome analyses using data on ACEi/ARB use at 3 months, the outcome analyses were censored at 3 months. A two-tailed P-value < 0.05 was considered statistically significant. All analyses were performed using R: a Language and Environment for Statistical Computing, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of the 2399 patients enrolled, 1605 (67%) were hospitalized at the time of enrolment. Baseline characteristics per quintile of FGF23 are presented in Table 1. Median FGF23 was 218.0 [117.1–579.3] RU/ml. Patients with a higher FGF23 level (i.e. being in a higher quintile of FGF23) were older, more often female, had a higher NYHA class, lower blood pressure, higher heart rate, and more signs of congestion (all $P < 0.005$). The prevalence of all signs and symptoms of congestion, i.e. oedema, orthopnoea, jugular venous pressure (JVP), and hepatomegaly were greater in patients with higher FGF23 levels. In addition, patients with higher FGF23 levels were more likely to be hospitalized with worsening heart failure, had worse renal function, higher (NT-pro)BNP, and renin levels (all $P < 0.001$). Also, these patients less frequently used ACEi or ARBs and beta-blockers, and a significantly lower percentage used target doses of both drugs.

Correlates of log transformed FGF23 in multivariable linear regression are presented in Supplementary table 1. The multivariable model had an overall r^2 of 0.459, and the variables showing the strongest association with higher log FGF23 levels were higher NT-proBNP, the presence of atrial fibrillation and the presence of oedema. Also, higher aldosterone levels were independently associated with higher log FGF23 levels.

3.1. FGF23 and therapy optimization

Higher levels of FGF23 were associated with lower rates of ACEi/ARB and beta-blocker use at baseline (Table 1). Also, patients with a higher FGF23 level less frequently used guideline-recommended doses of ACEi/ARBs and beta-blockers (Table 1). Furthermore, higher FGF23