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Fibroblast Growth Factor-23 and Cardiorenal Interactions

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Abstract

Background: Animal models implicate FGF-23 as a direct contributor to adverse cardiorenal interactions such as sodium avidity, diuretic resistance, and neurohormonal activation, but this has not been conclusively demonstrated in humans. Therefore, we aimed to evaluate whether FGF-23 is associated with parameters of cardiorenal dysfunction in humans with heart failure, independent of confounding factors.

Methods: 199 outpatients with heart failure undergoing diuretic treatment at the Yale Transitional Care Center were enrolled and underwent blood collection, and urine sampling before and after diuretics.

Results: FGF-23 was associated with several metrics of disease severity such as higher home loop diuretic dose and NT-proBNP, and lower estimated glomerular filtration rate, serum chloride, and serum albumin. Multivariable analysis demonstrated no statistically significant association

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between FGF-23 and sodium avidity measured by fractional excretion of sodium, or proximal or distal tubular sodium reabsorption, either before diuretic administration or at peak diuresis ($p \geq 0.11$ for all). Likewise, FGF-23 was not independently associated with parameters of diuretic resistance (diuretic excretion, cumulative urine and sodium output, and loop diuretic efficiency [$p \geq 0.33$ for all]) or neurohormonal activation (plasma or urine renin [$p \geq 0.36$ for all]). Moreover, the upper boundary of the 95% confidence interval of all the partial correlations were ≤.30, supporting the lack of meaningful correlations. FGF-23 was not associated with mortality in multivariable analysis ($p=0.44$).

Conclusion: FGF-23 was not meaningfully associated with any cardiorenal parameter in patients with heart failure. While our methods cannot rule out a small effect, FGF-23 is unlikely to be a primary driver of cardio-renal interactions.

Keywords

cardiorenal interactions; heart failure; FGF-23

Introduction

Cardiorenal syndrome is characterized by perturbations in sodium avidity, diuretic resistance, and neurohormonal activation. (1–6) Though several biomarkers have been studied in patients with cardiorenal dysfunction, few have emerged as having an independent role in its pathogenesis. (7, 8) Fibroblast Growth Factor-23 (FGF-23) is produced by osteocytes and primarily regulates phosphate homeostasis by suppressing sodium-phosphate cotransporters in the proximal tubule of the kidney, decreasing phosphate reabsorption. (9–11) FGF-23 has recently been proposed as a potential driver of cardiorenal dysfunction through its association with processes outside of phosphate homeostasis and has been shown to be an independent predictor of worse outcomes in patients with heart failure. (12–15)

Animal data support the hypothesis that FGF-23 influences key cardiorenal parameters. In murine models, FGF-23 increases proximal tubular sodium reabsorption and regulates distal sodium reabsorption through the sodium-chloride cotransporter (NCC). In addition, animal studies suggest an indirect effect on the epithelial sodium channel (ENaC). (16, 17) A strong association between FGF-23 and the renin-angiotensin-aldosterone system (RAAS) has been described, with some data supporting FGF-23 as a direct regulator of RAAS. (18–21) Even direct cardiac effects have been described in animal models. (22–24)

Although animal models implicate FGF-23's direct contribution to cardiorenal interactions, this has not been conclusively demonstrated in humans, with some data indicating a non-causal association between FGF-23 and cardiovascular outcomes. (25, 26) Therefore, we sought to better understand whether FGF-23 is independently associated with parameters of cardiorenal dysfunction in humans with heart failure, or if its association with cardio-renal dysfunction could be explained by confounding factors.

Methods

Population

The data, analytical methods, and study materials can be made available on request to other researchers for purposes of reproducing the results or replicating the procedure. Requests will be considered only for qualified investigators and should be made to the corresponding author.

This cohort prospectively enrolled 199 outpatients with heart failure who were referred for specialty treatment or seen in post-hospital follow-up at the Yale Transitional Care Center (YTCC). Patients were included if they had a clinical diagnosis of heart failure and were referred to this heart failure specialty clinic. This outpatient clinic focuses on volume management of ambulatory patients with heart failure. This study complied with the Declaration of Helsinki, all patients provided written informed consent, and the study was approved by the Yale Institutional Review Board.

Data collection

All patients were instructed to hold their morning diuretic dose before presenting to the YTCC. Weight, vital signs, and baseline urine samples were obtained at the YTCC before any medications were administered. Patients who were determined euvolemic by the on-site clinician received oral torsemide at their equivalent home loop diuretic dose. Alternatively, patients deemed to be volume overloaded received intravenous bumetanide at a dose chosen by the clinician. Blood and spot urine samples were acquired at time of peak diuresis (approximately 1.5 hours after diuretic was given) and from the total urine output over the following <6 hours. Urine concentrations of torsemide and bumetanide were measured in peak diuresis samples.

Assays

A Randox RxDaytona automated clinical chemistry analyzer was used to measure urine and serum electrolytes using ion-selective electrodes (Randox Laboratories). Creatinine and cystatin C were measured using Randox reagents as per the manufacturer's instructions (Randox Laboratories). Creatinine measurements are standardized to National Institute of Standards and Technology reference material (SRM 967). Assignment of cystatin C calibrators has been performed at Randox Laboratories by latex-enhanced immunoturbidimetry, with reference to material standardized against the International Federation of Clinical Chemistry Reference Standard. FGF-23 was measured in plasma on the Mesoscale Platform (Meso Scale Diagnostics, Gaithersburg, MD) as per manufacturer's instructions; it was measured either pre-diuretic in patients receiving IV diuretic or 1.5 hours following loop diuretic administration in patients receiving oral diuretics. Total Renin (R&D Systems, Minneapolis, USA) and active renin (ALPCO, Salem, NH, USA) were analyzed using commercially available ELISA kits. The total renin immunoassay kit from R&D systems recognizes both active renin and prorenin. The mean lower limit of detection is 4.43 pg/mL for total renin and 0.81 pg/mL for active renin. Plasma aldosterone level was measured by radioimmunoassay kit from Alpco (Alpco, Salem, NH) as per manufacturer's instructions. The lower limit of detection is 7 pg/ml. Endogenous lithium concentrations

in serum and urine samples were measured using a Thermo Element-XR magnetic sensor inductively coupled plasma mass spectrometer at the Yale Metal Geochemistry Center. Bumetanide and torsemide in urine were measured using liquid chromatography mass spectrometry. Details of assays used to measure urine and serum lithium as well as urine bumetanide and torsemide have been previously detailed. (5)

Definitions and calculations

Loop diuretic doses were converted to furosemide equivalents: 1 mg bumetanide = 20 mg torsemide = 40 mg intravenous furosemide = 80 mg oral furosemide. The Chronic Kidney Disease Epidemiology Collaboration equation using creatinine and cystatin C was used to estimate glomerular filtration rate (eGFR).(27) The urinary Na/K ratio was calculated and considered as a marker of aldosterone activity. The fractional excretions of sodium (FENa), chloride (FECl), potassium (FEK) and lithium (FELi) were calculated as fractional excretion of $X = (X_{urine}/X_{serum}) \times (Cr_{serum}/Cr_{urine}) \times 100$. FELi is considered the gold standard for *in vivo* assessment of proximal tubular and loop of Henle sodium handling. FELi means an increase in the delivery of sodium, or a reduced sodium reabsorption at the thick ascending limb of the loop of Henle. Therefore, sodium reabsorbed in the distal tubule was estimated as distal reabsorption = (1-FENa) - (1-FELi).

To approximate the concentration of diuretic reaching the luminal target, we used the ratio of loop diuretic to creatinine in the spot urine sample (expressed as nanograms of drug to milligrams of creatinine) at 1.5 hours post-diuretic administration. This value was divided by the dose of loop diuretic, and it was termed dose-adjusted estimated diuretic excretion. To compare patients receiving different diuretics, urinary diuretic excretion was normalized to administered furosemide equivalents by dividing the quantity of loop diuretic in the urine by the published urinary clearance of the drug (50% for bumetanide and 17% for torsemide) and then, converting to furosemide equivalents as described above. (28, 29)

Diuretic efficiency was calculated as the increase in sodium output per doubling of the loop diuretic dose centered on a dose of 40 mg of intravenous furosemide equivalents: diuretic efficiency = (mmol Na output) / [$\log_2$ (administered loop diuretic dose) – 4.32]. Doses ≤20 mg were winsorized to 40 mg to avoid negative values. (5)

Statistical analysis

Continuous variables with approximately normal distributions are presented as mean ± standard deviations, and those with skewed distributions are shown as median (quartile 1 – quartile 3). Categorical values are presented as percentages. Differences between groups were evaluated with Student *t*-test for normally distributed continuous variables, Mann–Whitney U test for skewed continuous variables, and chi-square tests for categorical variables. Associations of FGF-23 with cardiorenal parameters were examined in univariable linear regression, and variables with skewed distribution were log-transformed to approximate normal distribution. We next used multivariable linear regression to determine whether any associations of log-FGF-23 with each cardiorenal parameter were independent of conventional demographic and clinical parameters as covariates (age, sex, race, systolic blood pressure, home loop diuretic dose, serum chloride, serum albumin,

eGFR, NT-proBNP, left ventricular ejection fraction and administered loop diuretic dose). In these models, the partial correlation coefficients were shown as an attempt to estimate the correlation that would be observed if the effects of all other variables were removed. In addition, analyses were repeated with FGF-23 included as a dichotomous variable based on its median value (283 pg/mL) rather than as a continuous variable. Multiple imputation was performed for covariates when missingness was less than 10%. No covariates had more than 10% of data missing. No imputation method was used for FGF-23 or any of the cardiorenal parameters. The number of observations for each of the models is shown in the supplemental table I. Statistical significance was defined as a p value <0.05. All analyses were performed using Stata SE, version 14.0 (StataCorp, College Station, TX).

Results

Population

We included 199 patients (age 66±14 years; female 41%). Of these, 54% were judged to be volume overloaded and thus received intravenous bumetanide. In general, higher FGF-23 was associated with more severe heart failure parameters as reflected by higher doses of loop diuretic administered during the study, higher home loop diuretic dose, lower eGFR, lower serum chloride, lower serum albumin and higher NT-proBNP; Table 1.

Basal sodium avidity

In univariable analysis, FGF-23 was not statistically associated with baseline (pre-diuretic) FELi (sodium exiting the loop of Henle) and FENa (net sodium excreted in the urine) (both p >0.05), and the correlation with distal tubular sodium reabsorption was r = 0.23 (p=0.015); Figure 1. However, after adjusting for clinical parameters of heart failure severity, all associations weakened and were no longer statistically significant (p > 0.3 for all). When FGF-23 was analyzed as a binary variable dichotomized on its median value, there were no differences in any of the above mentioned cardiorenal parameters after multivariable adjustment (p > 0.3 for all; supplemental table II).

Sodium handling during peak diuresis and diuretic resistance

After loop diuretic administration, FGF-23 was not associated with FELi, FENa, and distal tubular sodium reabsorption (p > 0.25 for all); Figure 1. Likewise, FGF-23 did not correlate with total urine output (p = 0.28). FGF-23 was associated with peak diuretic excretion (r=0.17, p=0.04) and total sodium output (r=−0.19, p=0.01); Figure 2. FGF-23 was also associated with loop diuretic efficiency (r = −0.44, p<0.001). However, after adjusting for parameters of heart failure severity, all associations were attenuated and lost statistical significance (p ≥ 0.10 for all); Table 2. FGF-23 based on its median value was not significantly different for any of the above-mentioned parameters after multivariable adjustment (p > 0.10 for all); supplemental table II.

Neurohormonal activation

In univariable analysis, FGF-23 was associated with plasma total (r=0.16, p=0.04) and active renin (r=0.25, p=0.001), and urine total renin (r=0.22, p=0.01); Table 2 and Figure 2. FGF-23 was not statistically associated with the basal urinary Na/K ratio, and the

correlation with the urinary Na/K ratio at peak diuresis was r = −0.31 (p<0.001). After adjusting for parameters of heart failure, all associations became weaker and lost statistical significance (p ≥ 0.10 for all); Table 2. When RAAS inhibitor medications were included in the models associations remained non-statistically significant (p > 0.10 for all). FGF-23 based on its median value was not statistically different for any neurohormonal parameter after multivariable adjustment (p > 0.1 for all); supplemental table II.

Other parameters

In multivariable analysis, FGF-23 was not statistically associated with FECl or total chloride output in the baseline or peak diuresis sample (p > 0.10 for both); Table 2. Likewise, in multivariable analysis, FGF-23 was not associated with the baseline FEK, peak diuresis FEK, and total potassium output (p > 0.2 for all). Among these numerous parameters, FGF-23 was only independently associated with eGFR (partial correlation −0.32, p < 0.001). All the analyses shown in table 2 were repeated in subgroups of patients with or without preserved ejection fraction. Among these, only plasma active renin was independently associated with FGF-23; however, this was a negative association implying higher FGF-23 levels at lower plasma active renin (partial correlation −.31, p=.01). All other analysis showed similar results in that no statistically significant associations were found between FGF-23 and cardiorenal parameters (p>0.05 for all).

Survival

After a median follow-up of 2.9 years, 88 deaths occurred in our cohort. In univariable analysis with FGF23 as a continuous variable, each 2-fold higher FGF-23 concentration was associated with worse survival [hazard ratio (HR) 1.47, 95% confidence interval (CI) 1.24–1.74, p<0.001]. When dichotomized at the median, the higher FGF-23 category had a two-fold mortality rate [HR=2.20, 95% CI 1.39–3.49, p<0.001; respectively]. However, after adjusting for clinical parameters of heart failure severity (age, sex, race, systolic blood pressure, home loop diuretic dose, serum chloride, serum albumin, eGFR, NT-proBNP, and left ventricular ejection fraction), associations of FGF-23 as a continuous or dichotomous variable dramatically attenuated and lost statistical significance (HR 1.11, 95% CI 0.85–1.44, p=0.44; HR 1.05, 95% CI 0.52–2.10, p=0.90; respectively).

Discussion

In this study, we analyzed whether FGF-23 independently influences cardiorenal interactions in humans with heart failure. This study supports three principal conclusions. 1) In univariable analyses, FGF-23 was not associated with sodium avidity, and it was only weakly correlated with diuretic efficiency and neurohormonal activation. 2) However, after adjusting for basic clinical variables, FGF-23 was not statistically significantly associated with any cardiorenal parameter including: a) baseline sodium avidity, b) peak diuresis sodium handling, c) diuretic efficiency, and d) neurohormonal activation. 3) In addition, the association of FGF-23 with survival was significantly attenuated after adjusting for the same basic clinical indicators of heart failure severity. As such, these findings do not support FGF-23 as an independent contributor to cardiorenal interactions in humans with

heart failure. Rather, these results suggest that the apparent associations of FGF-23 with cardiorenal parameters and outcomes are driven by confounding, rather than causality.

Increased sodium avidity and diuretic resistance are key components of heart failure pathophysiology. (4, 6) This phenomenon might occur due to increased sodium reabsorption from the proximal tubule or the loop of Henle or, more commonly, due to compensatory distal tubular sodium reabsorption. (5) In this study, FGF-23 was not independently associated with reduced diuretic delivery – which could account for insufficient sodium excretion at the loop of Henle. Likewise, we found no statistically significant associations between FGF-23 and diuretic failure at the loop of Henle (FELi), distal tubular sodium reabsorption, or net sodium excreted. Thus, despite those mechanisms of sodium retention suggested by animal models, our findings did not support the role of FGF-23 driving sodium retention in humans with heart failure.

RAAS activation is one of the most important pathophysiologic mechanisms in heart failure. (30) In this study, while we did observe weak correlation between FGF-23 and plasma or urine renin, these associations were fully attenuated and lost statistical significance in multivariable analyses. Likewise, no significant associations were found between FGF-23 and aldosterone or the urinary sodium-to-potassium ratio in multivariable analysis. This argues against an independent role for FGF-23 on RAAS activation in humans with heart failure. Hypochloremia has been independently associated with worse outcomes, neurohormonal activation, and diuretic resistance, with renal chloride wasting as a candidate mechanism for low plasma chloride levels. (31, 32) As with markers of neurohormonal activation, we observed no association between FGF-23 and several metrics of chloride wasting. However, we did observe an independent association between FGF-23 and eGFR, which is a well-understood association in humans. (11, 33) This finding likely indicates that our analysis could capture valid associations and was not overly weakened by adjustment for clinical covariates.

FGF-23 has been hypothesized to be a direct contributor to cardiorenal interactions based on animal studies. (16–18, 34) However, to the best of our knowledge, this is the first study to test this hypothesis in humans with heart failure. The incongruency between these previous studies and our findings may have several explanations, including the well-known limitations of applying animal models to human systems. Although FGF-23 appeared to be an independent predictor of cardiovascular outcomes in humans in previous studies (12, 13, 15), newer data have questioned these conclusions, and a recent meta-analysis did not support a causal relationship between FGF-23 and cardiovascular disease risk. (25, 26)

Limitations of this study include its cross-sectional and observational design. We did not have strict prospective criteria for the diagnosis of heart failure; however, all patients had a clinical diagnosis of heart failure, were on chronic treatment with loop diuretics, and 95% had elevated levels of natriuretic peptides according to international guidelines on the diagnosis of heart failure (NT-proBNP >125 pg/ml) and the other 5% had a body mass index >40 kg/m2; thus, we think this data is enough to satisfy the criteria for heart failure. Although the YTCC study is designed to study in-depth physiologic information on cardiorenal interactions, the absence of urinary catheters and relatively short observation

period highlight the real-world limitations of this study setting. We did not specifically measure c-terminal FGF-23, which could have shown stronger associations with cardiorenal parameters, though we believe the assay used to be appropriate. We measured FGF-23 only once during the study, and although it is not likely substantial changes in plasma concentration would occur after 1.5 hours, it would have been informative to measure it two times to determine if the change from baseline to peak diuresis was associated with the cardiorenal parameters. This cohort included heart failure patients with high disease-severity treated in an outpatient clinical setting, and findings may not generalize to more advanced forms of heart failure. It might still be possible that the study was underpowered given the number of patients and covariables in the multivariable models; however, these associations are unlikely to be strong. The study was also underpowered for survival analysis. This was a post-hoc analysis and thus, results should be interpreted cautiously. Finally, no formal definition of cardiorenal syndrome exists; thus, even though we analyzed several well-studied parameters of cardiorenal pathophysiology, we cannot exclude that some unmeasured parameter might be associated with FGF-23.

In conclusion, FGF-23 was not independently associated with several well-established cardiorenal parameters including sodium avidity, diuretic resistance, and neurohormonal activation. As such, our findings do not support FGF-23 as an independent contributor to cardiorenal interactions in humans with heart failure and highlight the caution necessary in translating observations from animal studies to human disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICTS OF INTEREST

Dr. Testani reports grants and personal grants and personal fees from 3ive labs, personal fees from Bayer, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Bristol Myers Squibb, personal fees from Astra Zeneca, personal fees from Novartis, personal fees from Cardionomic, personal fees from MagentaMed, grants and personal fees from Reprieve medical, grants and personal fees from FIRE1, personal fees from W.L. Gore, grants and personal fees from Sanofi, grants and personal fees from Sequana Medical, grants from Otsuka, grants from Abbott, grants and personal fees from Merck, personal fees from Windtree Therapeutics, personal fees from Lexicon pharmaceuticals, personal fees from Regeneron, outside the submitted work; In addition, Dr. Testani has a patent Treatment of diuretic resistance US20200079846A1 issued to Yale and Corvidia Therapeutics Inc, a patent Methods for measuring renalase WO2019133665A2 issued to Yale, and a patent Treatment of diuretic resistance pending to Reprieve Medical. Dr. Rao has a patent Treatment of diuretic resistance US20200079846A1 issued to Yale and Corvidia Therapeutics Inc with royalties paid to Yale University, Dr. Rao, and Dr. Testani and a patent Methods for measuring renalase WO2019133665A2 issued to Yale. Dr. Rao reports personal fees from Translational Catalyst. Dr. Wilson reports research support from Boehringer Ingelheim, Amgen, and AstraZeneca. Dr Ivey-Miranda reports personal fees from AstraZeneca and Moksha8. All the other authors have nothing to disclose.

Abbreviations

CI	confidence interval
eGFR	estimated glomerular filtration rate
FECl	fractional excretion of chloride
FEK	fractional excretion of potassium
FELi	fractional excretion of lithium
FENa	fractional excretion of sodium
FGF-23	Fibroblast Growth Factor-23
HR	hazard ratio
RAAS	renin-angiotensin-aldosterone system
YTCC	Yale Transitional Care Center

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What is new?

- FGF-23 has been proposed as a contributor of adverse cardio-renal interactions directly influencing parameters such as sodium avidity and neurohormonal activation. However, it is unclear if FGF-23 is associated with parameters of cardiorenal dysfunction in humans with heart failure, independent of confounding factors.
- In the current study we found, after adjusting for potential confounders that FGF-23 was no longer meaningfully associated with cardiorenal parameters such as sodium avidity, diuretic resistance, or neurohormonal activation. Therefore, our study argues against a predominant role of FGF-23 in cardiorenal syndrome in humans with heart failure.

What are the clinical implications?

- Identification of the underlying mechanisms for cardiorenal syndrome could lead to development of therapeutic options. FGF-23 has been proposed as one such mediator based on studies in animal models.
- In the present study, FGF-23 was not meaningfully associated with cardio-renal interactions in humans with heart failure; therefore, it is unlikely that FGF-23 is a primary driver of cardio-renal interactions.
- As such, these findings argue against FGF-23 as a potential therapeutic target for the treatment of cardiorenal syndrome.

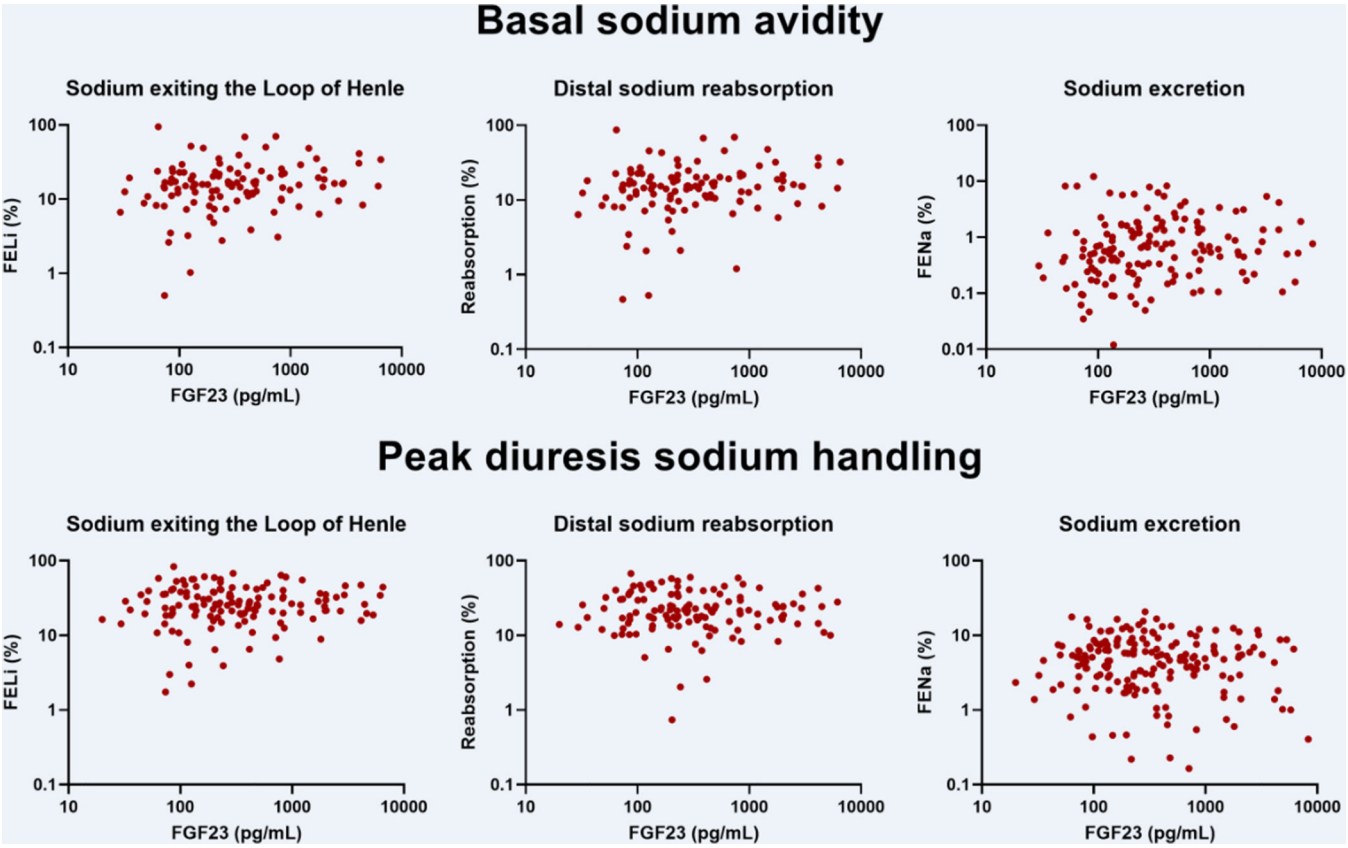

Figure 1.

The correlations between FGF-23 and baseline FELi, reabsorption, and FENa were .15 (p=.11), .23 (p=.015), and .15 (p=.058), respectively. For peak diuresis FELi, reabsorption, and FENa, correlations were .10 (p=.26), .01 (p=.93), and −.07 (p=.33), respectively.

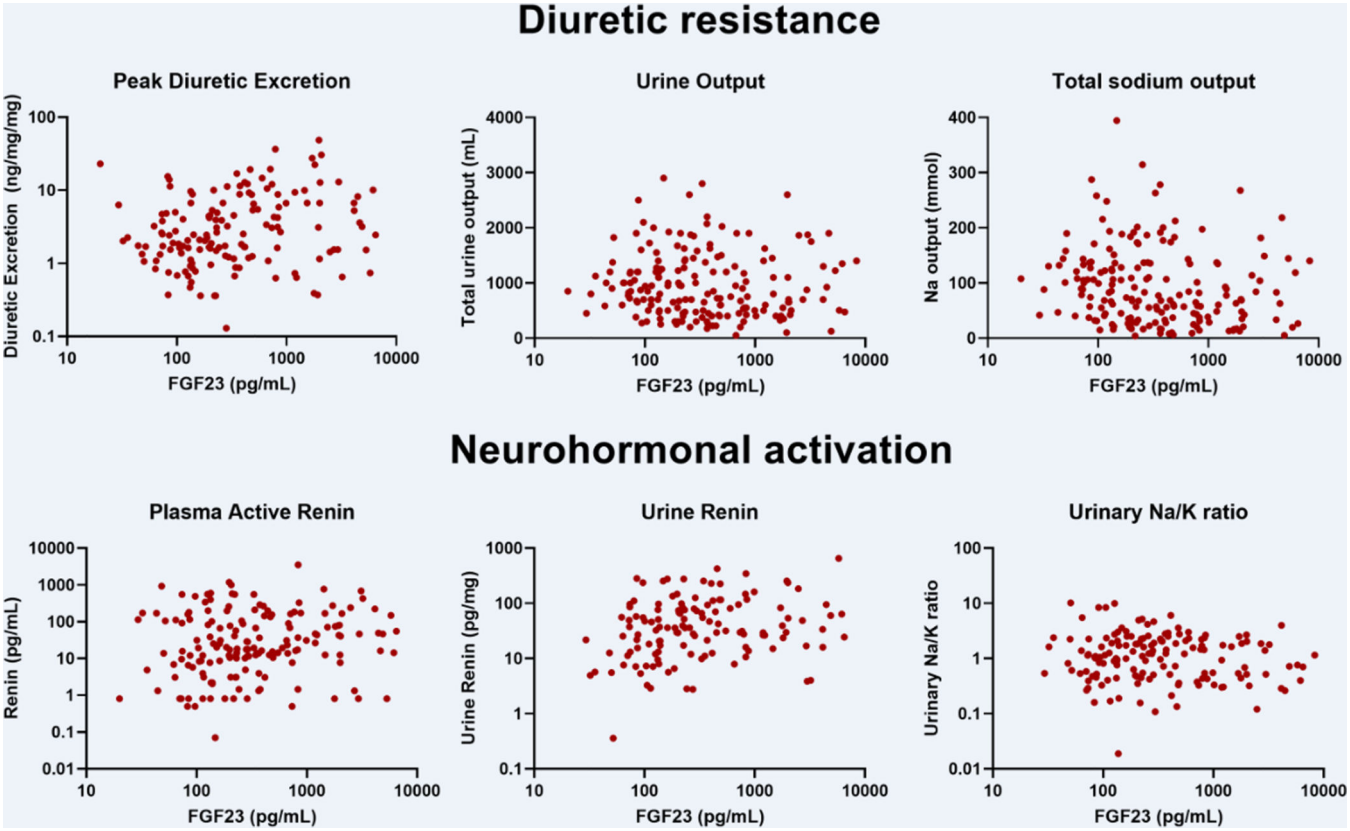

Figure 2.

The correlations between FGF-23 and peak diuretic excretion, urine output, total sodium excretion, plasma active renin, urine renin, and the urinary Na/K ratio were −.31 (p<.001), −.08, (p=.28), −.19 (p=.01), 0.16 (p=.04), 0.22 (p=.01), and −.10 (p=.20), respectively.

Table 1.

Baseline characteristics of patients.

	Overall n = 199	Lower FGF-23 (≤283 pg/mL) n = 100	Higher FGF-23 (>283 pg/mL) n = 99	p
Age (years)	66 ± 14	65 ± 14	68 ± 13	0.17
Female (%)	41	41	40	0.93
Black race (%)	30	36	24	0.07
Diabetes (%)	51	55	46	0.23
Hypertension (%)	85	87	83	0.41
Left ventricular ejection fraction (%)	44 ± 17	46 ± 17	43 ± 17	0.24
Preserved ejection fraction (≥50%)	42%	45%	39%	0.44
Home loop diuretic dose (mg of furosemide equivalent)	118 ± 100	96 ± 79	140 ± 113	0.003
Study diuretic IV bumetanide (%)	54	45	64	0.01
Loop diuretic dose administered during the study (furosemide equivalent in mg)	160 (40 – 280)	80 (40 – 160)	200 (80 – 400)	<0.001
Systolic blood pressure (mmHg)	127 ± 19	129 ± 19	125 ± 19	0.076
eGFR (ml/min/1.73m^2)	38 (26 – 63)	49 (35 – 74)	28 (22 – 47)	<0.001
Serum sodium (mmol/L)	137.3 ± 4.0	137.9 ± 3.8	136.8 ± 4.1	0.06
Serum chloride (mmol/L)	98.3 ± 5.1	99.3 ± 4.8	97.4 ± 5.2	0.008
Serum potassium (mmol/L)	4.14 ± 0.54	4.19 ± 0.50	4.09 ± 0.57	0.20
Serum albumin (g/dL)	3.74 ± 0.43	3.81 ± 0.45	3.67 ± 0.41	0.02
NT-proBNP (pg/mL)	1850 (607–4500)	927 (340 – 2370)	3415 (1150 – 6380)	<0.001

Table 2.

Univariable and multivariable associations of FGF-23 with cardiorenal parameters.

	Univariable	Adjusted for eGFR	MV model
	r (95% CI)	r' (95% CI)	r' (95% CI)
Baseline (pre-diuretic) sodium avidity			
FELi, % †	0.15 (−0.02, 0.33)	0.06 (−0.13, 0.25)	0.03 (−0.17, 0.24)
FENa, % †	0.15 * (0.01, 0.30)	−0.11 (−0.26, 0.05)	−0.04 (−0.20, 0.13)
Distal Tubular Reabsorption	0.23 * (0.05, 0.41)	0.13 (−0.06, 0.32)	0.10 (−0.09, 0.29)
Sodium handling during peak diuresis and diuretic resistance			
FELi (peak diuresis sample), % †	0.10 (−0.05, 0.25)	−0.01 (−0.16, 0.14)	0.03 (−0.13, 0.19)
FENa (peak diuresis sample), % †	−0.07 (−0.24, 0.09)	−0.13 (−0.29, 0.02)	−0.14 (−0.30, 0.02)
Distal Tubular Reabsorption (peak diuresis sample)	0.01 (−0.15, 0.16)	−0.03 (−0.17, 0.12)	−0.01 (−0.18, 0.16)
Urine output, mL	−0.06 (−0.21, 0.10)	0.08 (−0.06, 0.23)	0.06 (−0.11, 0.24)
Peak diuretic excretion †	0.17 * (0.00, 0.33)	0.08 (−0.09, 0.25)	0.06 (−0.10, 0.21)
Total sodium output, mmol	−0.17 * (−0.30, −0.03)	−0.01 (−0.15, 0.13)	0.00 (−0.19, 0.19)
Loop Diuretic efficiency †	−0.44 * (−0.56, −0.32)	−0.32 * (−0.44, −0.19)	−0.09 (−0.26, 0.09)
Neurohormonal activation			
Plasma active renin (pg/mL) †	0.16 * (0.00, 0.33)	0.07 (−0.08, 0.23)	−0.09 (−0.27, 0.10)
Plasma total renin (pg/mL) †	0.25 * (0.11, 0.39)	0.14 (0.00, 0.29)	0.03 (−0.16, 0.22)
Urine renin (pg/mL/mg creatinine) †	0.22 * (0.04, 0.40)	0.15 (−0.03, 0.33)	0.03 (−0.20, 0.26)
Plasma aldosterone (pg/mL) †	0.29 * (0.14, 0.45)	0.22 * (0.05, 0.38)	0.08 (−0.10, 0.27)
Baseline (pre-diuretic) Urinary Na/K ratio †	−0.10 (−0.25, 0.04)	−0.14 (−0.29, 0.00)	−0.08 (−0.25, 0.09)
Peak diuresis Urinary Na/K ratio †	−0.31 * (−0.46, −0.15)	−0.22 * (−0.37, −0.08)	−0.14 (−0.30, 0.01)
Other parameters			
Baseline (Pre-diuretic) FECl, % †	0.23 * (0.08, 0.37)	−0.03 (−0.19, 0.12)	0.06 (−0.13, 0.24)
Peak diuresis FECl, % †	−0.04 (−0.21, 0.13)	−0.09 (−0.24, 0.06)	−0.13 (−0.28, 0.02)
Total chloride output, mmol †	−0.19 * (−0.34, −0.04)	−0.01 (−0.17, 0.14)	−0.05 (−0.23, 0.14)
Baseline (Pre-diuretic) FEK, % †	0.40 * (0.25, 0.54)	0.10 (−0.07, 0.27)	0.09 (−0.10, 0.29)
Peak diuresis FEK, % †	0.20 * (−0.02, 0.42)	0.02 (−0.18, 0.22)	−0.06 (−0.24, 0.11)
Total potassium output, mmol †	0.06 (−0.12, 0.24)	0.15 (−0.01, 0.30)	0.11 (−0.06, 0.28)
eGFR (ml/min/1.73m2) †	−0.43 * (−0.54, −0.32)	---	−0.33 * (−0.47, −0.19)

Each row represents three different models. The first column shows the cardiorenal parameter which was the dependent variable. The second column shows the correlation in the first model (univariable analysis). The third column shows the r' (partial correlation) of the second model adjusting for eGFR. The fourth column (MV: multivariable model) shows the r' of the third model adjusting for eGFR, NT-proBNP, loop diuretic dose, age, sex, race, systolic blood pressure, home loop diuretic dose, serum chloride, serum albumin, and left ventricular ejection fraction.

For diuretic efficiency, multivariable analysis also included intravenous vs. oral administration. For the peak diuresis parameters, multivariable analysis included loop diuretic dose administered during the study. Diuretic efficiency is mmol of sodium per doubling loop diuretic dose. Peak

diuretic excretion refers to dose-adjusted estimated urine diuretic excretion (nanograms per milligram creatinine per milligram administered diuretic).

*$p < 0.05$.

†Transformed variable.