INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 07 Aug 2026
Revised: 26 Aug 2026
Accepted: 07 Sep 2026
Published: 27 Sep 2026

Volume 12 Issue 09, 2026
Page No - 275-285
DOI - 10.55640/ijmsdh-12-09-33

Article Citation: Norkhonov, A. G., & Gadaeva, N. A. (2026). Alpha-Klotho, FGF-23, and Calcium-Phosphate Product Across Renal Function Strata in Chronic Heart Failure: Associations with Cardiac Remodeling and Six-Month Treatment Response. International Journal of Medical Science and Dental Health, 12(09), 275-285. https://doi.org/10.55640/ijmsdh-12-09-33

Alpha-Klotho, FGF-23, and Calcium-Phosphate Product Across Renal Function Strata in Chronic Heart Failure: Associations with Cardiac Remodeling and Six-Month Treatment Response

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Abstract

Background: Renal dysfunction in chronic heart failure (CHF) is accompanied by disturbances in mineral metabolism and may promote vascular calcification. The alpha-Klotho/FGF-23 axis is a potential molecular link between declining renal filtration, phosphate handling, and adverse cardiovascular remodeling.

Objective: To evaluate circulating alpha-Klotho, fibroblast growth factor-23 (FGF-23), and the calcium-phosphate product (Ca×P) across cystatin C-based estimated glomerular filtration rate (eGFR) strata in patients with CHF, examine their associations with cardiac remodeling, and describe six-month biomarker changes during guideline-directed therapy with or without adjunctive sevelamer carbonate.

Methods: This clinical cohort included 120 patients with ischemic heart disease-related NYHA functional class II–III CHF. Patients were stratified by cystatin C-based eGFR into <60 mL/min/1.73 m² (n=55), 60–90 mL/min/1.73 m² (n=45), and >90 mL/min/1.73 m² (n=20). Serum alpha-Klotho, FGF-23, cystatin C, vitamin D, NT-proBNP, aldosterone, calcium, phosphorus, electrolytes, and echocardiographic parameters were assessed. Ca×P was calculated as a research surrogate of mineral-related calcification propensity. Fifteen patients in each of the two lower-eGFR strata received sevelamer carbonate in addition to standard CHF therapy; follow-up was performed at six months. Treatment

allocation procedures were not described in the source dissertation.

Results: Alpha-Klotho decreased stepwise with renal impairment (0.52±0.02, 0.84±0.01, and 0.98±0.03 ng/mL across the <60, 60–90, and >90 eGFR strata, respectively; P<0.001), whereas FGF-23 increased markedly (404.9±17.2, 118.5±3.7, and 84.07±2.01 pg/mL; P<0.001). Ca×P was highest in the lowest-eGFR group (3.51±0.04 vs. 2.84±0.02 vs. 2.24±0.02 $mmol^2/L^2$; P<0.001). Alpha-Klotho correlated inversely with Ca×P in the eGFR <60 (r=−0.53, P<0.001) and 60–90 (r=−0.47, P<0.001) strata, but not significantly in the >90 stratum (r=−0.24, P>0.05). Lower eGFR was also accompanied by lower LVEF and higher left ventricular myocardial mass. At six months in the eGFR <60 stratum, the subgroup receiving sevelamer had numerically higher alpha-Klotho (0.68 vs. 0.61 ng/mL), lower Ca×P (3.02 vs. 3.27 $mmol^2/L^2$), lower FGF-23 (271.9 vs. 356.7 pg/mL), and higher vitamin D (37 vs. 33 ng/mL) than the standard-therapy subgroup. Direct between-subgroup significance tests were not reported.

Conclusion: The alpha-Klotho/FGF-23 axis is strongly altered as renal filtration declines in CHF and is accompanied by greater mineral-metabolism disturbance and adverse cardiac remodeling. The inverse relationship between alpha-Klotho and Ca×P was most evident in patients with impaired renal filtration. Exploratory six-month data suggest a potentially favorable mineral-metabolic profile with adjunctive sevelamer in the lowest-eGFR stratum, but randomized and independently validated studies are required.

Keywords: Chronic heart failure; Alpha-Klotho; FGF-23; Cystatin C; Estimated glomerular filtration rate; Calcium-phosphate product; Cardiorenal syndrome; Vascular calcification; Sevelamer carbonate

Introduction

Background

Chronic heart failure (CHF) is a major cause of morbidity, recurrent hospitalization, and mortality worldwide. Renal dysfunction is common in CHF and independently predicts adverse outcomes, reflecting the bidirectional hemodynamic, neurohormonal, inflammatory, and metabolic interactions that characterize the cardiorenal syndrome [1,2]. Although creatinine remains widely used, cystatin C may provide a more sensitive estimate of glomerular filtration in settings where muscle mass and other nonrenal determinants can confound creatinine-based assessment [3].

Progressive renal impairment also alters phosphate handling, vitamin D metabolism, and endocrine signaling within the FGF-23–Klotho axis. FGF-23, predominantly produced by osteocytes, increases phosphaturia and suppresses active vitamin D synthesis. Its canonical renal actions depend on alpha-Klotho, a transmembrane coreceptor that is highly expressed in the kidney [4–7]. In chronic kidney disease, circulating FGF-23 typically rises as renal function declines, whereas renal and soluble Klotho availability decreases [6–8].

The cardiovascular implications of this axis extend beyond mineral balance. Experimental and clinical data associate increased FGF-23 with left ventricular hypertrophy, myocardial fibrosis, diastolic dysfunction, and adverse outcomes in heart failure [4,5,9]. Conversely, Klotho deficiency has been linked to vascular calcification and cardiovascular injury, while preserved or higher Klotho may exert protective effects through anti-inflammatory, antioxidative, and mineral-regulatory mechanisms [7,8,10].

Disordered calcium-phosphate metabolism may further promote ectopic mineral deposition. The calcium-phosphate product (Ca×P) is not a substitute for direct vascular imaging and is not a stand-alone clinical diagnostic criterion; however, it can be used as an integrative research measure of the combined mineral load relevant to calcification biology [11–13]. In CHF complicated by renal dysfunction, simultaneous assessment of Klotho, FGF-23, Ca×P, and cardiac remodeling may therefore provide a more integrated view of the cardiorenal-mineral phenotype.

The present study aimed to compare alpha-Klotho, FGF-23, mineral-metabolism indices, neurohormonal biomarkers, and echocardiographic characteristics across three cystatin C-based eGFR strata in patients with ischemic CHF. A secondary exploratory objective was to describe six-month changes in the lower-eGFR strata during guideline-directed CHF therapy with or without adjunctive sevelamer carbonate.

Materials and Methods

Study Design and Participants

This manuscript is based on a clinical dissertation study performed at Tashkent State Medical University. The cohort comprised 120 patients with chronic heart failure secondary to ischemic heart disease and NYHA functional class II–III symptoms. Cystatin C-based eGFR was used to define three prespecified renal-function strata: Group I, eGFR <60 mL/min/1.73 m^2 (n=55); Group II, eGFR 60–90 mL/min/1.73 m^2 (n=45); and Group III, eGFR >90 mL/min/1.73 m^2 (n=20). Mean ages were 65.9±1.3, 66.0±1.3, and 67.6±2.2 years, respectively.

Eligibility Criteria

The inclusion criterion documented in the dissertation was ischemic heart disease-related CHF with NYHA functional class II or III. Exclusion criteria included acute myocardial infarction, unstable angina, arterial hypotension, severe

arrhythmias, second- or third-degree atrioventricular block, congenital heart disease, acute cerebrovascular events, autoimmune or diffuse connective-tissue disease, active acute or chronic inflammatory disease, liver disease with hepatic failure, kidney disease considered unrelated to CHF, bronchial asthma, chronic obstructive pulmonary disease, severe respiratory failure, psychiatric disease, malignancy, alcoholism, and other major comorbid conditions.

Clinical and Echocardiographic Assessment

Clinical evaluation included medical history, physical examination, blood pressure, electrocardiography, and transthoracic echocardiography. Echocardiography was performed with a GE Healthcare Vivid T8 system using M-mode and two-dimensional imaging. The evaluated variables included left ventricular end-diastolic and end-systolic dimensions and volumes, interventricular septal and posterior wall thicknesses, left ventricular ejection fraction (LVEF; Simpson method), transmitral E and A velocities and the E/A ratio, and left ventricular myocardial mass calculated using the Devereux formula.

Laboratory Measurements

Laboratory testing was performed before treatment and at six months. Serum cystatin C was measured by an immunoturbidimetric method, and eGFR was calculated using the 2012 CKD-EPI cystatin C approach. Serum alpha-Klotho and FGF-23 were measured using enzyme-linked immunosorbent assays. Aldosterone was measured using a DBC Aldosterone ELISA (Canada), NT-proBNP using Vector-Best reagents (Russia), and 25-hydroxyvitamin D using Monobind reagents on a Mindray MR-96A platform. Calcium, phosphorus, sodium, potassium, and routine biochemical parameters were also measured.

Calcium-Phosphate Product

Ca×P was calculated as serum total calcium (mmol/L) multiplied by serum inorganic phosphorus (mmol/L), yielding $mmol^2/L^2$. In this study it was used as a research surrogate reflecting the combined calcium-phosphate burden relevant to ectopic mineralization. Because no direct vascular calcification imaging endpoint was reported, Ca×P should not be interpreted as a direct measurement of vascular calcium.

Treatment and Six-Month Follow-up

All patients received guideline-directed multidrug CHF therapy documented in the dissertation, comprising renin-angiotensin system inhibition (ACE inhibitor/ARB or a neprilysin-containing regimen), a beta-blocker, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor as clinically appropriate. In Group I and Group II, 15 patients per group additionally received the phosphate-binding agent sevelamer carbonate at individually selected doses. The remaining patients received standard therapy alone (Group I: n=40; Group II: n=30); Group III (n=20) received standard therapy. The source dissertation does not describe random sequence generation, allocation concealment, or blinding. Consequently, the treatment component is reported as an exploratory observational comparison rather than a randomized trial.

Statistical Analysis

The dissertation reports analyses performed in SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as M±m; the source text refers to these values as means with standard deviations, although the notation should be verified against the original dataset before journal submission. Between-group comparisons used Kruskal-Wallis or Mann-Whitney procedures for continuous variables and chi-square or Fisher exact tests for categorical variables. Pearson correlation analysis was used to assess associations. A two-sided $P<0.05$ was considered statistically significant. No unreported statistical tests were reconstructed for this manuscript.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Ethics Committee Termez Branch, Tashkent State Medical University. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants were informed about the objectives, procedures, potential risks, and intended scientific use of the collected data. Written informed consent was obtained from all participants before enrollment. Participant confidentiality was maintained throughout the study.

Results

Study Population

The cohort included 120 patients. Group I (eGFR <60 mL/min/1.73 m^2) comprised 55 patients (20 men and 35 women), Group II (eGFR 60–90) comprised 45 patients (20 men and 25 women), and Group III (eGFR >90) comprised 20 patients (11 men and 9 women). Age, sex distribution, and baseline systolic and diastolic blood pressure did not differ significantly among groups.

Table 1. Baseline clinical characteristics by renal-function stratum

Characteristic	eGFR <60 (n=55)	eGFR 60–90 (n=45)	eGFR >90 (n=20)	Reported comparison
Age, years	65.9 ± 1.3	66.0 ± 1.3	67.6 ± 2.2	P>0.05
Male sex, n (%)	20 (36.3)	20 (44.4)	11 (55.0)	P>0.05
Female sex, n (%)	35 (63.7)	25 (55.6)	9 (45.0)	P>0.05
Systolic BP, mmHg	138.0 ± 2.4	137.5 ± 2.7	140.0 ± 4.9	P>0.05
Diastolic BP, mmHg	84.8 ± 1.2	82.8 ± 1.4	84.0 ± 2.1	P>0.05

Values are reproduced from the dissertation. BP, blood pressure; eGFR, estimated glomerular filtration rate.

Renal Function, Klotho–FGF-23 Axis, and Mineral Metabolism

Renal impairment was accompanied by a marked and graded shift in the Klotho–FGF-23 axis. Alpha-Klotho was lowest in Group I and increased across Groups II and III (0.52±0.02, 0.84±0.01, and 0.98±0.03 ng/mL; all reported pairwise P<0.001). FGF-23 showed the opposite pattern, with a more than threefold higher mean value in Group I than Group II and almost fivefold higher value than Group III (404.9±17.2, 118.5±3.7, and 84.07±2.01 pg/mL; P<0.001).

Cystatin C increased and vitamin D decreased as eGFR declined. Phosphorus and Ca×P were highest in Group I, whereas calcium was lowest. The Ca×P product rose from 2.24±0.02 mmol²/L² in Group III to 2.84±0.02 in Group II and 3.51±0.04 in Group I (P<0.001), indicating a progressively less favorable mineral profile with renal dysfunction.

Table 2. Renal, mineral, and neurohormonal biomarkers across eGFR strata

Parameter	eGFR <60	eGFR 60–90	eGFR >90	Reported significance
Cystatin C, mg/L	1.60 ± 0.03	1.05 ± 0.02	0.77 ± 0.01	All pairwise P<0.001
eGFR, mL/min/1.73 m²	47.02 ± 0.98	72.9 ± 1.3	100.9 ± 2.07	All pairwise P<0.001
Vitamin D, ng/mL	27.8 ± 0.6	34.7 ± 0.5	39.2 ± 0.6	All pairwise P<0.001
Alpha-Klotho, ng/mL	0.52 ± 0.02	0.84 ± 0.01	0.98 ± 0.03	All pairwise P<0.001
FGF-23, pg/mL	404.9 ± 17.2	118.5 ± 3.7	84.07 ± 2.01	P<0.001
NT-proBNP, pg/mL	733.0 ± 63.4	282.1 ± 10.6	257.3 ± 16.5	Group I vs II/III P<0.001
Aldosterone, pg/mL	181.8 ± 4.97	178.8 ± 2.5	141.4 ± 3.0	I vs III and II vs III P<0.001
Calcium, mmol/L	2.10 ± 0.02	2.20 ± 0.005	2.26 ± 0.01	P<0.001

Phosphorus, mmol/L	1.67 ± 0.02	1.28 ± 0.01	0.99 ± 0.01	All pairwise P<0.001
Potassium, mmol/L	4.40 ± 0.04	4.30 ± 0.05	4.10 ± 0.02	I/II vs III P<0.001
Sodium, mmol/L	135.7 ± 0.8	137.7 ± 0.5	139.2 ± 0.5	P<0.05 to P<0.001
Ca×P, mmol²/L²	3.51 ± 0.04	2.84 ± 0.02	2.24 ± 0.02	P<0.001

Values are source-reported means ± M±m. FGF-23, fibroblast growth factor-23; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ca×P, calcium-phosphate product.

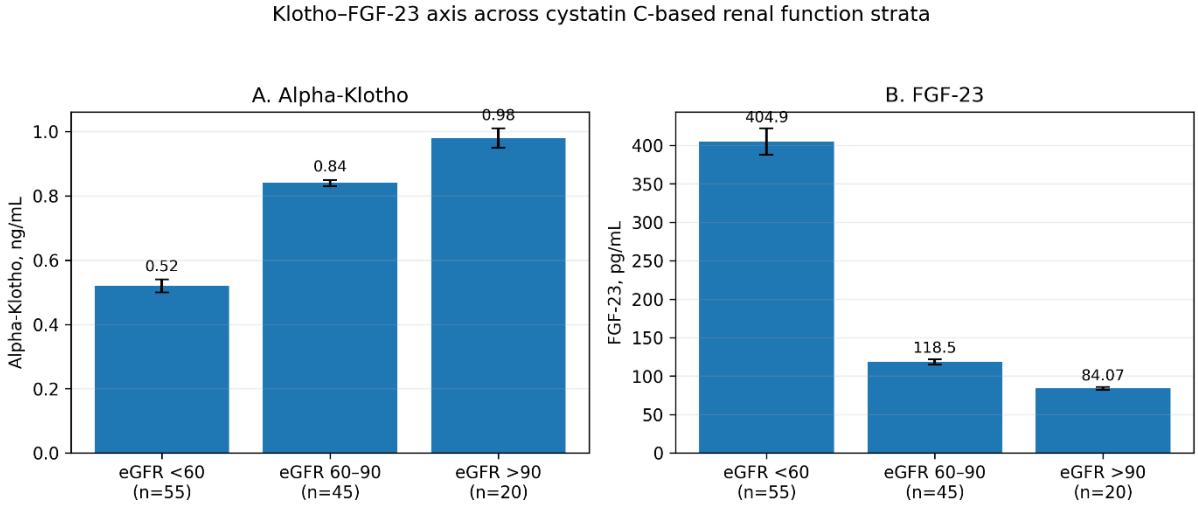

Figure 1. Alpha-Klotho and FGF-23 concentrations across cystatin C-based eGFR strata. Error bars reproduce the dispersion/error values reported in the dissertation. All between-stratum differences were reported as P<0.001.

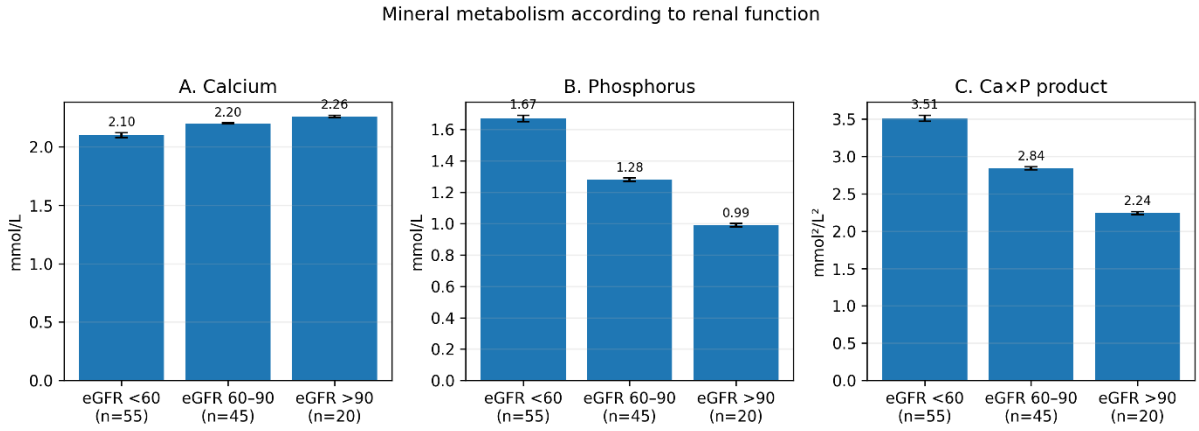

Figure 2. Serum calcium, phosphorus, and Ca×P product across cystatin C-based eGFR strata. The progressively higher phosphorus and Ca×P values accompany declining renal filtration (reported P<0.001).

Echocardiographic Characteristics

Selected cardiac structural and functional indices worsened with lower renal filtration. LVEF was 49.1±1.5% in Group I, 51.8±1.3% in Group II, and 54.04±1.3% in Group III; the difference between Groups I and III was significant (P<0.05). The E/A ratio was lowest in Group I (0.70±0.02) compared with Group II (0.85±0.03; P<0.001) and Group III (1.15±0.15; P<0.01). Left ventricular myocardial mass was substantially greater in Group I (259.0±4.9 g) than in Group II (227.3±4.7 g) or Group III (223.7±5.6 g; P<0.001).

Table 3. Selected echocardiographic parameters by renal-function stratum

Parameter	eGFR <60	eGFR 60–90	eGFR >90	Reported significance
LV end-diastolic diameter, cm	5.4 ± 0.1	5.3 ± 0.1	5.05 ± 0.1	I vs III P<0.05
LV end-systolic volume, mL	69.7 ± 4.6	63.7 ± 4.9	57.6 ± 2.8	I vs III P<0.05
LVEF, %	49.1 ± 1.5	51.8 ± 1.3	54.04 ± 1.3	I vs III P<0.05
E/A ratio	0.70 ± 0.02	0.85 ± 0.03	1.15 ± 0.15	I vs II P<0.001; I vs III P<0.01
Interventricular septum, cm	1.20 ± 0.03	1.20 ± 0.02	1.14 ± 0.02	II vs III P<0.05
LV myocardial mass, g	259.0 ± 4.9	227.3 ± 4.7	223.7 ± 5.6	I vs II/III P<0.001

LV, left ventricular; LVEF, left ventricular ejection fraction.

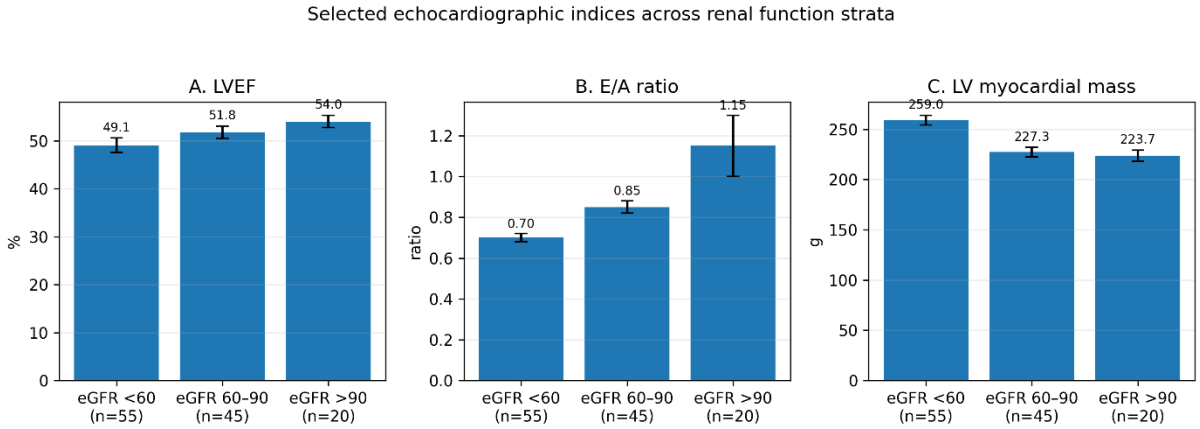

Figure 3. Selected echocardiographic indices across renal-function strata. Lower eGFR was accompanied by lower LVEF and E/A ratio and higher left ventricular myocardial mass.

Correlations of Alpha-Klotho with Cardiorenal and Mineral Markers

In Group I, alpha-Klotho correlated positively with eGFR (r=0.26, P<0.05) and vitamin D (r=0.29, P<0.05), and inversely with cystatin C (r=−0.28, P<0.05) and FGF-23 (r=−0.28, P<0.05). Similar but slightly weaker significant associations were reported in Group II. In Group III, correlations between alpha-Klotho and the studied biochemical variables were weak and not statistically significant.

The strongest mineral association was observed between alpha-Klotho and Ca×P. This relationship was moderately inverse in Group I (r=−0.53, P<0.001) and Group II (r=−0.47, P<0.001), whereas it was weaker and nonsignificant in Group III (r=−0.24, P>0.05).

Table 4. Pearson correlations between alpha-Klotho and selected biomarkers

Variable	eGFR <60, r (P)	eGFR 60–90, r (P)	eGFR >90, r (P)
eGFR	0.26 (<0.05)	0.22 (<0.05)	0.08 (>0.05)
Vitamin D	0.29 (<0.05)	0.15 (<0.05)	0.13 (>0.05)
Cystatin C	−0.28 (<0.05)	−0.24 (<0.05)	−0.09 (>0.05)
FGF-23	−0.28 (<0.05)	−0.26 (<0.05)	−0.14 (>0.05)
NT-proBNP	−0.13 (>0.05)	−0.15 (>0.05)	−0.23 (>0.05)
Aldosterone	−0.18 (>0.05)	−0.15 (>0.05)	−0.15 (>0.05)
Ca×P	−0.53 (<0.001)	−0.47 (<0.001)	−0.24 (>0.05)

Correlation coefficients and P values are reproduced from the dissertation.

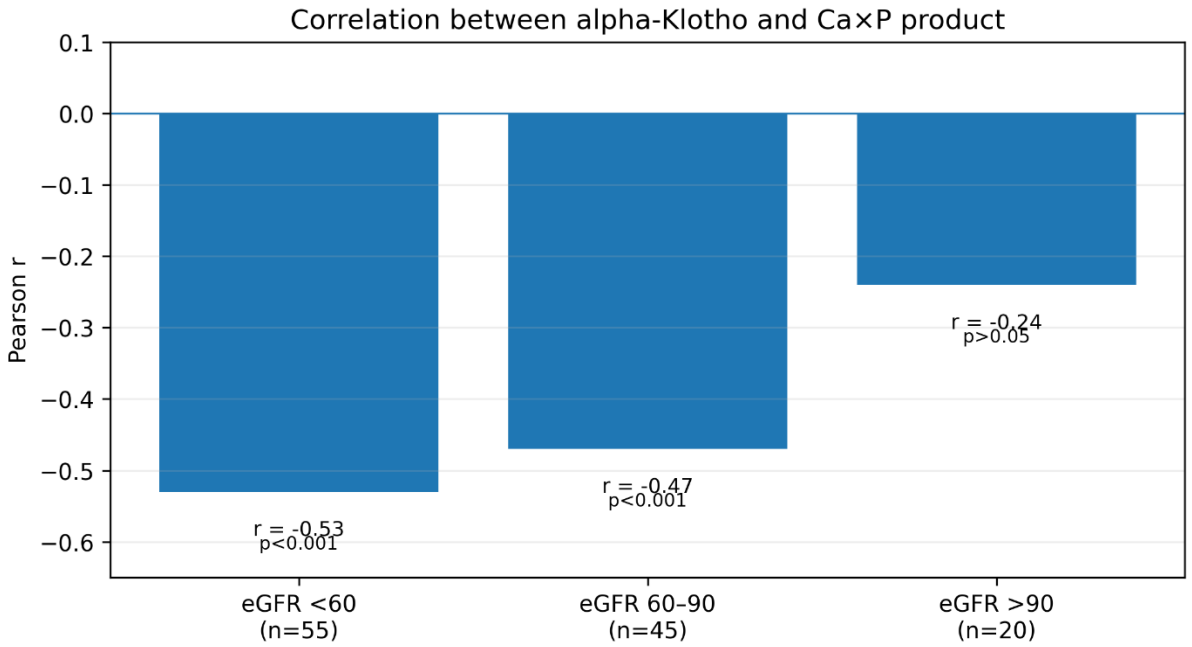

Figure 4. Correlation between alpha-Klotho and Ca×P by renal-function stratum. The inverse association was strongest in patients with reduced or mildly reduced eGFR and was not significant when eGFR was >90 mL/min/1.73 m².

Six-Month Treatment Response

At six months, all renal-function strata showed favorable changes in several mineral and neurohormonal markers during standard CHF therapy. The dissertation additionally reports 15 patients in Group I and 15 patients in Group II who received sevelamer carbonate. The most pronounced numerical separation between treatment subgroups was observed in Group I (eGFR <60 mL/min/1.73 m²).

In Group I, the overall pretreatment alpha-Klotho concentration was 0.52±0.02 ng/mL. At six months it was 0.68±0.02 ng/mL in the sevelamer subgroup (reported within-group P<0.001) and 0.61±0.08 ng/mL in the standard-therapy subgroup (P<0.01). Ca×P decreased from an overall pretreatment value of 3.51±0.04 to 3.02±0.03 mmol²/L² with sevelamer and 3.27±0.08 with standard therapy (both reported P<0.001 versus pretreatment). FGF-23 fell to 271.9±11.8 pg/mL with sevelamer and 356.7±18.3 pg/mL with standard therapy from an overall pretreatment value of 404.9±17.2 pg/mL. Vitamin D increased to 37±0.7 and 33±0.8 ng/mL, respectively, from 28±0.6 ng/mL.

Because the dissertation does not provide subgroup-specific baseline values or direct between-subgroup statistical comparisons, these treatment findings should be interpreted as descriptive and hypothesis-generating. They do not establish an independent treatment effect of sevelamer.

Table 5. Six-month biomarker outcomes in the eGFR <60 mL/min/1.73 m² stratum

Outcome	Pretreatment overall (n=55)	6 mo standard therapy (n=40)	6 mo standard + sevelamer (n=15)	Source-reported within-group significance
Alpha-Klotho, ng/mL	0.52 ± 0.02	0.61 ± 0.08	0.68 ± 0.02	Standard P<0.01; sevelamer P<0.001
Ca×P, mmol²/L²	3.51 ± 0.04	3.27 ± 0.08	3.02 ± 0.03	Both P<0.001
FGF-23, pg/mL	404.9 ± 17.2	356.7 ± 18.3	271.9 ± 11.8	Standard P<0.01; sevelamer P<0.001
Aldosterone, pg/mL	181.8 ± 4.9	141.2 ± 4.1	126.7 ± 3.4	Standard P<0.01; sevelamer P<0.001
Vitamin D, ng/mL	28 ± 0.6	33 ± 0.8	37 ± 0.7	Both P<0.001

Pretreatment values are reported for the full eGFR <60 stratum, not separately by treatment subgroup. No direct standard-therapy-versus-sevelamer P values were provided.

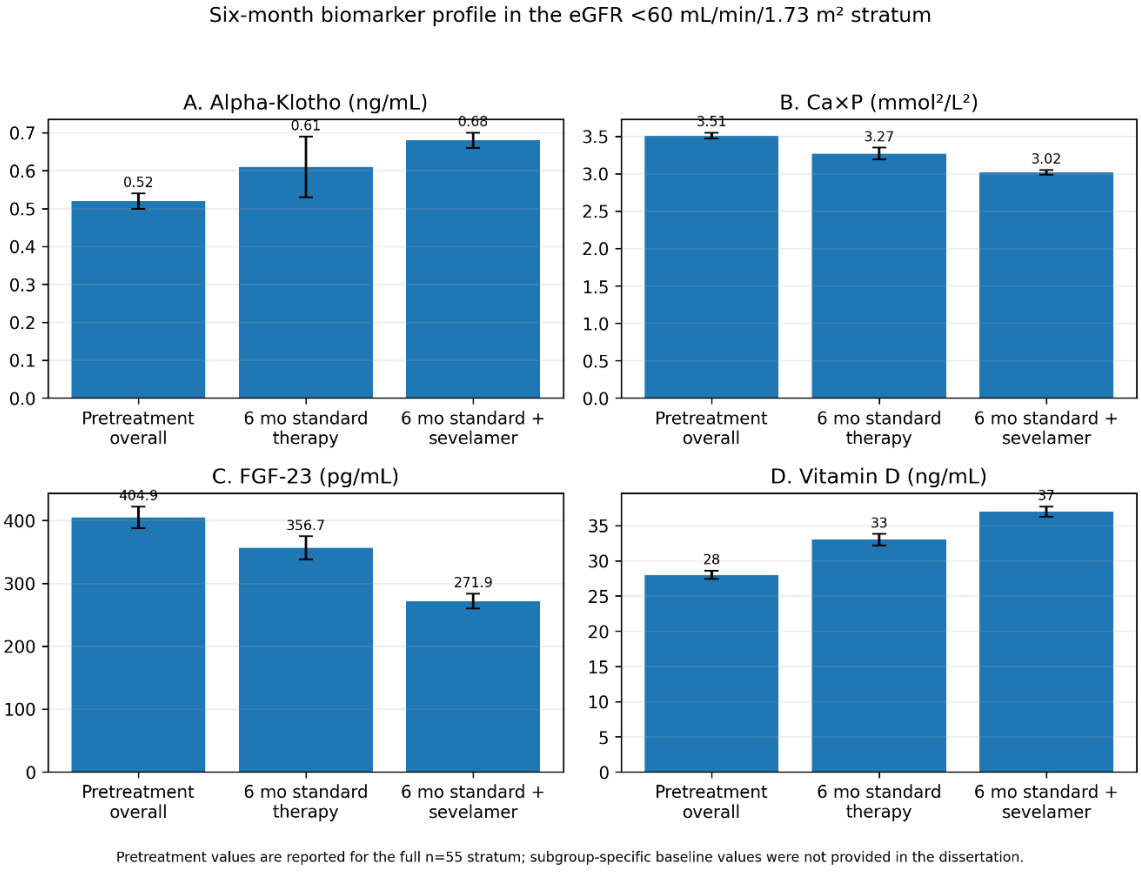

Figure 5. Six-month biomarker profile in the eGFR <60 mL/min/1.73 m² stratum. Pretreatment values represent the full stratum; subgroup-specific baseline values were not available. The figure is therefore descriptive and does not represent a randomized or adjusted treatment comparison.

Discussion

The principal finding of this study is a coherent, graded alteration of the alpha-Klotho/FGF-23 axis across cystatin C-based renal-function strata in patients with CHF. Patients with eGFR <60 mL/min/1.73 m² had the lowest circulating alpha-Klotho, the highest FGF-23, the highest phosphorus and Ca×P, and the lowest vitamin D. These biochemical differences were accompanied by a less favorable cardiac phenotype, including lower LVEF, lower E/A ratio, and greater left ventricular myocardial mass. Together, the findings support the concept that worsening renal filtration in CHF is associated not only with impaired excretory function but also with a broader cardiorenal-mineral disorder.

The marked rise in FGF-23 with declining eGFR is consistent with its physiological role as an early adaptive response to reduced phosphate excretion. Increased FGF-23 may initially help maintain phosphate homeostasis, but sustained elevations have been associated with left ventricular hypertrophy, myocardial fibrosis, heart failure severity, and adverse clinical outcomes [4–6,9]. Faul and colleagues demonstrated a direct hypertrophic effect of FGF-23 on the myocardium, while subsequent clinical studies linked higher FGF-23 to cardiac remodeling and prognosis [5,9,14]. The nearly fivefold difference between the lowest- and highest-eGFR strata in the present cohort underscores the magnitude of this endocrine response in cardiorenal disease.

Alpha-Klotho demonstrated the opposite pattern. Klotho is highly expressed in the kidney and functions as a coreceptor for canonical FGF-23 signaling, while soluble Klotho has been implicated in vascular protection, antioxidative signaling, and suppression of calcification [7,8,10]. The reduction from 0.98 ng/mL in patients with preserved eGFR to 0.52 ng/mL in those with eGFR <60 suggests that declining renal function is accompanied by substantial loss of this potentially protective signal. The simultaneous elevation of FGF-23 and reduction of Klotho is biologically important because it may represent both impaired renal Klotho production and relative resistance to FGF-23 signaling.

The inverse relationship between alpha-Klotho and Ca×P was particularly notable. Correlations were moderate and highly significant in the two lower-eGFR strata, but weak and nonsignificant in patients with eGFR >90. This pattern suggests that the Klotho–mineral relationship becomes more apparent when renal reserve is reduced. Experimental studies support an anti-calcific role of Klotho, and Klotho deficiency has been shown to potentiate vascular calcification in chronic kidney disease [10]. Recent clinical and meta-analytic data also support associations between soluble Klotho, CKD-mineral bone disorder, and atherosclerotic burden [15,16].

Nevertheless, Ca×P in this dissertation is a calculated research surrogate rather than a direct imaging measure of vascular calcification. KDIGO guidance emphasizes serial assessment of calcium and phosphorus in CKD-mineral and bone disorder and does not establish Ca×P alone as a diagnostic test for vascular calcification [11]. Accordingly, the observed Ca×P gradients should be interpreted as evidence of increasingly unfavorable mineral balance and calcification propensity, not proof of anatomical vascular calcium deposition.

The cardiac findings provide a clinically relevant context for the biochemical axis. Patients with the lowest eGFR had greater left ventricular mass and lower systolic and diastolic functional indices. FGF-23 has been associated with left ventricular hypertrophy and fibrosis, while lower Klotho has been reported in patients with cardiovascular and renal disease [5,9,14]. However, the present study is observational and cannot determine whether the Klotho/FGF-23 disturbance is causal, a consequence of renal dysfunction, or a marker of the same underlying disease severity.

The six-month treatment data are exploratory. Guideline-directed CHF therapy was accompanied by favorable changes in Klotho, FGF-23, Ca×P, aldosterone, and vitamin D. In the eGFR <60 stratum, patients receiving adjunctive sevelamer had numerically larger changes in several markers than those receiving standard therapy alone. This is biologically plausible because phosphate binding can reduce intestinal phosphate absorption and may thereby influence FGF-23 and downstream mineral signaling. However, subgroup-specific baseline values, allocation methods, adherence data, and direct between-group statistical comparisons were not reported. Therefore, the results should not be interpreted as proof of sevelamer efficacy in CHF.

Future studies should prospectively randomize patients with CHF and renal dysfunction to standardized mineral-directed strategies, prespecify Klotho and FGF-23 endpoints, include direct vascular calcification imaging or validated calcification-propensity testing, and use repeated-measures models adjusted for age, sex, diabetes, kidney function, background medication, and phosphate intake. Such studies would clarify whether modifying mineral metabolism can produce clinically meaningful cardiorenal benefits beyond contemporary guideline-directed heart failure therapy.

Clinical Implications and Study Limitations

The findings support integrated assessment of renal function and mineral-endocrine biomarkers in research on CHF-associated cardiorenal dysfunction. The alpha-Klotho/FGF-23 axis may be particularly informative when eGFR falls below 90 mL/min/1.73 m², where the study observed stronger relationships with cystatin C, vitamin D, and Ca×P. At present, however, these

biomarkers should be viewed as investigational rather than replacements for established renal and heart-failure markers.

Several limitations should be acknowledged. First, the study was observational and the source dissertation does not document randomization, allocation concealment, or blinding for sevelamer treatment. Second, treatment-subgroup baseline characteristics and subgroup-specific baseline biomarker values were not reported, preventing assessment of baseline balance or adjusted treatment effects. Third, the source provides summary statistics rather than patient-level data and uses the notation M±m ambiguously. Fourth, vascular calcification was not directly quantified by computed tomography, radiography, ultrasound, or another anatomical method; Ca×P was used as a research surrogate. Fifth, albuminuria, parathyroid hormone, dietary phosphate exposure, and several other CKD-mineral bone disorder variables were not reported. Sixth, no multivariable regression was described to determine whether Klotho or FGF-23 was independently associated with cardiac remodeling after accounting for renal function and other confounders. Finally, ethics approval details and the informed-consent statement were not included in the supplied dissertation and must be confirmed before submission.

Conclusions

In patients with NYHA class II–III chronic heart failure, declining cystatin C-based eGFR was associated with lower circulating alpha-Klotho, markedly higher FGF-23, lower vitamin D, higher phosphorus and Ca×P, and less favorable left ventricular structure and function. Alpha-Klotho showed a significant inverse relationship with Ca×P in patients with eGFR <90 mL/min/1.73 m², supporting a close interaction between renal Klotho biology and mineral-metabolism disturbance in the cardiorenal continuum. Six-month observational data suggested numerically greater improvement in several mineral-endocrine markers among selected patients with eGFR <60 receiving adjunctive sevelamer, but causal efficacy cannot be established from the available data. Prospective randomized studies with direct vascular calcification assessment and validated longitudinal statistics are required.

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