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Hormonal Role of Fibroblast Growth Factor-23 (FGF23) in Early Renal Dysfunction Association with Biochemical Markers of Phosphate and Renal Function

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Abstract:

Background: Fibroblast growth factor 23 (FGF23) has been identified as one of the first hormonal changes occurring in early stages of kidney disease as well as chronic kidney disease (CKD) and could be promising biomarker in the early stages of kidney diseases

Methodology: This case-control study enrolled 80 patients with early renal dysfunction and 20 healthy controls and measured the levels of FGF23 in relation to serum urea, creatinine and phosphate (PO_4), estimated glomerular filtration rate (GFR) from the period of November 2025 to March 2026.

Results: The patients showed a significant increase in serum urea, creatinine, phosphate, and FGF23 and a significant decrease in GFR (all $p \leq 0.03$). Compared to the controls (49.77 ± 2.24 vs. 38.77 ± 4.19 pg/mL, $p = 0.03$) and at a stage of only moderate phosphate elevation, circulating FGF23 was significantly higher in patients. ROC analysis pinpointed a diagnostic threshold of 46.76 pg/mL (AUC = 0.66, $p = 0.009$). Given the absence of significant correlations with individual biochemical metrics and the analysis of FGF23 positioned as a hormonal sentinel of renal tubular phosphate stress, FGF23 is more likely an early-phase player and not a linear biochemical replacement.

Conclusion: In conclusion this study position FGF23 as an early hormonal marker of renal tubular phosphate stress and provides a clinically useful hormonal cutoff to advocate for the use of FGF23 in conjunction with the standard biochemical markers for early identification of renal impairment.

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الدور الهرموني لعامل نمو الخلايا الليفية(FGF23) 23 في الخلل الكلوي المبكر وعلاقته بالعلامات الحيوية الكيميائية للفوسفات ووظائف الكلى"

يسر حسام محمد

الخلاصة:

تم تحديد عامل نمو الخلايا الليفية(FGF23) 23 كواحد من اول التغيرات الهرمونية التي تحدث في المراحل المبكرة من امراض الكلى وكذلك امراض الكلى المزمنة (CKD)ويمكن ان يكون مؤشراً حيوياً واعداً في المراحل المبكرة من امراض الكلى.

العينات وطرق العمل:

أجريت هذه الدراسة من نوع الحالات والشواهد (Case–Control) وشملت 80 مريضًا يعانون من اختلال مبكر في وظائف الكلى، إلى جانب 20 فردًا سليمًا كمجموعة ضابطة. تم خلالها تقييم مستويات عامل نمو الخلايا الليفية 23 (FGF23) ومقارنتها مع مؤشرات وظائف الكلى التقليدية، بما في ذلك اليوريا والكرياتينين ومستوى الفوسفات (PO_4)، إضافةً إلى معدل الترشيح الكبيبي المُقدّر (GFR). وقد نُفذت الدراسة خلال الفترة الممتدة من نوفمبر 2025 إلى مارس 2026.

النتائج:

أظهرت نتائج المرضى ارتفاعًا معنويًا في مستويات اليوريا والكرياتينين والفوسفات، بالإضافة إلى عامل نمو الخلايا الليفية 23 (FGF23)، يقابله انخفاض معنوي في معدل الترشيح الكبيبي(GFR) ، وذلك بقيم دلالة إحصائية.($p \leq 0.03$)

وعند المقارنة مع المجموعة الضابطة، كانت مستويات FGF23 أعلى بشكل ملحوظ لدى المرضى (49.77 ± 2.24 مقابل 38.77 ± 4.19 بيكوغرام/مل، ($p = 0.03$)، حتى في المراحل التي يكون فيها ارتفاع الفوسفات متوسطًا فقط، مما يشير إلى أن زيادة FGF23 تحدث في مراحل مبكرة نسبيًا.

كما أظهر تحليل منحنى ROC أن القيمة الحدّية التشخيصية لـ FGF23 بلغت 46.76 بيكوغرام/مل($AUC = 0.66$) ، $p =$ (0.009)، ما يدعم قيمته كمؤشر تشخيصي.

وبالنظر إلى عدم وجود ارتباطات معنوية واضحة بين FGF23 والمؤشرات البيوكيميائية الفردية، يمكن اعتباره مؤشرًا هرمونيًا مبكرًا يعكس إجهاد النبيبات الكلوية المرتبط باضطراب توازن الفوسفات، وليس بديلاً خطيًا مباشرًا للمؤشرات التقليدية لوظائف الكلى.

الاستنتاج:

ختامًا، تُبرز هذه الدراسة عامل نمو الخلايا الليفية 23 (FGF23) كمؤشر هرموني مبكر يعكس إجهاد النبيبات الكلوية المرتبط باضطراب الفوسفات، كما تُقدّم قيمة حدّية ذات أهمية سريرية يمكن الاعتماد عليها. وعليه، يُوصى باستخدام FGF23 إلى جانب المؤشرات البيوكيميائية التقليدية لتعزيز الكشف المبكر عن القصور الكلوي.

1. Introduction

Chronic kidney disease leads to gradual loss of nephrons, disrupting systemic endocrine homeostasis, and causing hormonal changes that occur prior to clinical renal failure. One of the first changes observed, and one of the most important, is the disruption of the homeostasis of phosphate, controlled by a bone-derived hormone that is partially characterized and changes in its function remain elusive to researchers during the early stages of renal disease (Drüeke and Massy, 2012; Hum *et al.*, 2017) Fibroblast Growth Factor 23 (FGF23) has developed into the major hormonal controller of phosphate regulation in the kidneys, working through a highly controlled endocrine system that connects the sensory perception of minerals in the skeleton to the transport function of the renal tubules (Russo and Battaglia, 2011) FGF23 is produced by osteocytes and osteoblasts as a response to elevated levels of phosphates and 1,25-dihydroxyvitamin D_3, as well as dietary phosphate absorption. FGF23 targets the renal proximal tubule epithelium to reduce the activity of sodium-phosphate cotransporters and, at the same time, decreases the activity of renal 1α-hydroxylase in a coordinated response that decreases renal tubular reabsorption of phosphates and the bioactivation of vitamin D (Clinkenbeard and White, 2016) The endocrine axis of bone and kidney is a clear example of the physiological range of inter-organ communication and its dysfunction, particularly with respect to kidney disease, triggers a distinct and often severe range of dysregulation of minerals, with serious implications for the whole body. . Unlike traditional renal biomarkers, FGF23 indicates renal tubular stress before glomerular filtration metrics fall outside reference ranges. FGF23 increases prior to elevations in serum phosphate, parathyroid hormone, and creatinine, as nephron mass decreases, and phosphate handling impaired tubular. This phenomenon is known to occur long before those other biomarkers are clinically relevant. For this reason, FGF23 is a responsive marker in the early stages of renal tubule dysfunction (Yang *et al.*, 2016) In contrast, FGF23 is a pathobiological marker. FGF23 can promote renal tubular inflammation, reduce nitric oxide signaling in endothelial cells, cause left ventricular hypertrophy, and accelerate progressive CKD through tubule fibrosis. This systemic effect causes organ damage and is especially true of FGF23 that is above compensatory levels (Giuliani *et al.*, 2024) Under conditions of increasing renal loss of the receptor α-Klotho which is necessary for FGF23 receptor (FGFR1) complex formation and signaling (Faul *et al.*, 2011) the hormonal interplay with FGF23 becomes even more complex. As renal expression of α-Klotho diminishes with increasing nephron loss, FGF23 hormonal resistance occurs, a condition where despite the presence of a significantly elevated FGF23, the patient is biochemically-assessed as FGF23 resistant, and, to make matters even more complicated, there is a hormonal excess that increases off target organ dysfunction and alters the patient hormonal balance, all without restoring the organism phosphate balance (Seiler, Heine and Fliser, 2009) This lack of correlation between FGF23 levels and biological . Despite the extensive body of evidence linking FGF23 to the pathophysiology of CKD, multiple clinically pertinent aspects of its hormonal profile in early renal dysfunction remain elusive. In early-stage clinical cohorts, where the hormonal signal is present, the biochemical relationships between circulating FGF23 and standard markers of glomerular filtration and tubular phosphate handling are poorly defined. FGF23 potential as an independent early hormonal biomarker in comparison to established biochemical markers has also not been thoroughly investigated in this setting, including any formal diagnostic studies. Filling these gaps is clinically important, as the FGF23-triggered phosphate hormonal dysregulation is an early event that can be targeted by nephroprotective strategies prior to the development of irreversible tubular damage and CKD-MBD.

Aims of the study

This study aimed to characterize the hormonal profile of circulating FGF23 in early renal dysfunction and evaluate its biochemical correlations with glomerular filtration and phosphate metabolism.

2. Materials and Methods

2.1. Subjects and methods

This case-control study aims to describe the profile of the circulating FGF23 hormonal in early renal dysfunction in relation to some established markers of glomerular filtration and some markers/phosphate metabolism.

2.2. Participant and Sample Description

One hundred adult participants were divided into two groups as follows: 80 patients with renal dysfunction, and 20 controls who were healthy. Of the patient cohort, there were 52 females and 28 males, and in the control, there were 14 females and 6 males. For all participants, demographic parameters were captured, including age, sex, height, weight body mass index (BMI).

2.3. Sample Size and Power Analysis

The sample size was calculated with G* Power version 3.1.9.7, considering the independent samples t-test with a moderate effect size (d = 0.5), alpha error probability of 0.05, and statistical power of 80%, which is estimated to be 100 participants.

2.4. Inclusion and Exclusion Criteria

The study enrolled adult participants with Early Renal Dysfunction confirmed both clinically and biochemically, as well as healthy controls. Participants with autoimmune diseases, malignancies, or other systemic diseases that would confound the assessment of kidney biochemistry or alter circulating FGF23 levels were excluded.

2.5. Sample Collection

Venous blood samples were collected from all study participants. The serum was separated and processed for biochemistry by the standard operating procedure in the laboratory.

2.6. Biochemical Analysis

The serum biochemical parameters analyzed included urea, creatinine, the estimated glomerular filtration rate (GFR), Urea, Creatinine, phosphate (PO_4) and circulating FGF23 (pg/mL) for both groups.

2.7. Statistical Analysis

The analysis of statistical data was performed using IBM SPSS Statistics version 27 and GraphPad Prism version 10. Continuous variables were expressed as mean ± standard error (SE). For intergroup comparisons, independent samples t-test was performed. For correlation analysis, Spearman's rank correlation coefficient (r) was used. The diagnostic performance of FGF23 and biochemistry parameters was evaluated using the Receiver Operating Characteristic (ROC) curve analysis. Area under the curve (AUC), with 95% confidence interval, sensitivity, and 95% confidence interval, specificity, and optimal cut-off values were calculated using the Youden index. A p-value less than 0.05 was considered statistically significant.

Ethical Approval

The study followed ethical and institutional guidelines, and informed consent was obtained from participants prior to sample collection in the study.

3. Results

3.1. Demographic Characteristics

The mean age of the patients was significantly greater than that of the control group (67.36 ± 1.40 vs. 49.25 ± 3.59 years, $p < 0.001$). There were no statistically significant intergroup differences regarding height, weight, BMI, or gender ($p = 0.56, 0.38, 0.62, 0.67$), demonstrating appropriate anthropometric parity between groups. As illustrated in the Table1.

Table1: Demographic Characteristics of The Control and Patient Groups.

Variable	Control (n = 20)	Patient (n = 80)	P value
Age (years)	49.25 ± 3.59	67.36 ± 1.40	< 0.001
Height (cm)	163.85 ± 2.02	165.10 ± 0.93	0.56
Weight (kg)	75.50 ± 3.93	78.26 ± 1.24	0.38
BMI (kg/m²)	28.02 ± 1.30	28.64 ± 0.53	0.62
Female	14 (70.00%)	52 (65.00%)	0.67
Male	6 (30.00%)	28 (35.00%)	0.67
Data are presented as Mean ± SE or n (%). P-values were calculated using independent samples t-test for continuous variables and chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant.			

3.2. Biochemical Parameters

The biochemical profile of patients was indicative of early renal dysfunction. Compared to controls, the serum urea of patients was significantly higher (58.53 ± 1.59 vs. 31.46 ± 1.66 mg/dL, $p < 0.001$). Serum creatinine was higher in the patients compared to the controls (1.27 ± 0.04 vs. 0.74 ± 0.03 mg/dL, $p < 0.001$). Serum phosphate (PO_4) was also significantly elevated in the patients as compared to the controls (4.25 ± 0.08 vs. 3.38 ± 0.14 mg/dL, $p < 0.001$). In contrast, estimated GFR was significantly lower in the patient group compared to controls (56.45 ± 1.89 vs. 105.20 ± 2.82 mL/min/1.73m², $p < 0.001$). Circulating FGF23 was significantly higher in patients as compared to controls (49.77 ± 2.24 vs. 38.77 ± 4.19 pg/mL, $p = 0.03$), indicating an early hormonal dysregulation of the metabolism of phosphate, before the occurrence of overt mineral imbalances. As shown in Table2.

Table2: Biochemical Parameters of Interest in The Control and Patient Groups

Parameter	Control (n = 20)	Patient (n = 80)	P-value
Urea (mg/dL)	31.46 ± 1.66	58.53 ± 1.59	< 0.001
Creatinine (mg/dL)	0.74 ± 0.03	1.27 ± 0.04	< 0.001
GFR (mL/min/1.73m²)	105.20 ± 2.82	56.45 ± 1.89	< 0.001
PO_4 (mg/dL)	3.38 ± 0.14	4.25 ± 0.08	< 0.001
FGF23 (pg/mL)	38.77 ± 4.19	49.77 ± 2.24	0.03
Data are presented as Mean ± SE. P-values were calculated using independent samples t-test. A p-value < 0.05 was considered statistically significant.			

3.3. Diagnostic Performance and Correlation Analysis of FGF23 and Biochemical Markers

Receiver operating characteristic (ROC) analysis showed a discriminatory performance hierarchy among each of the studied biomarkers. Among the studied biomarkers, urea was able to achieve perfect discrimination (AUC=1.00, sensitivity 96.00%, specificity 98.00%, cutoff 42.75 mg/dL) followed by creatinine (AUC=0.97, sensitivity 88.80%, specificity 95.00%, cutoff 0.93 mg/dL) and phosphate (AUC=0.82, sensitivity 53.80%, specificity 95.00%, cutoff 4.25 mg/dL, all $p < 0.001$ respectively). GFR showed a negative ROC GFR (AUC=0.02) due to significantly low GFR values among the patients studied, when considering test directionality, this is statistically equivalent to near perfect discriminatory performance (sensitivity 98.00%, specificity 97.00%, $p < 0.001$). There was statistically significant, performance of diagnostic discrimination by circulating FGF23 (AUC=0.66, sensitivity 63.30%, specificity 65.00%, cutoff 46.76 pg/mL, p=0.009), and thus FGF23 should be considered a positive early-phase functional endocrine biomarker rather than a primary diagnostic biomarker. As reported in Fig.1. Among the patient subgroups, Spearman's correlation analysis showed that some biochemical and hormonal parameters are interrelated. Urea, on the one hand, showed a significant positive correlation with both creatinine ($r = 0.38$, $p < 0.001$) and PO_4 ($r = 0.28$, $p < 0.01$), as well as a significant negative correlation with GFR ($r = -0.53$, $p < 0.001$). Its correlation with FGF23, however, was non-significant ($r = -0.06$, p = ns). On the other hand, GFR showed a significant negative correlation with PO_4 ($r = -0.22$, $p < 0.05$) and FGF23 ($r = 0.06$, p = ns). PO_4 and FGF23 showed no significant correlation with the exception of one ($r = -0.04$, p = ns). As demonstrated in the Fig.1.

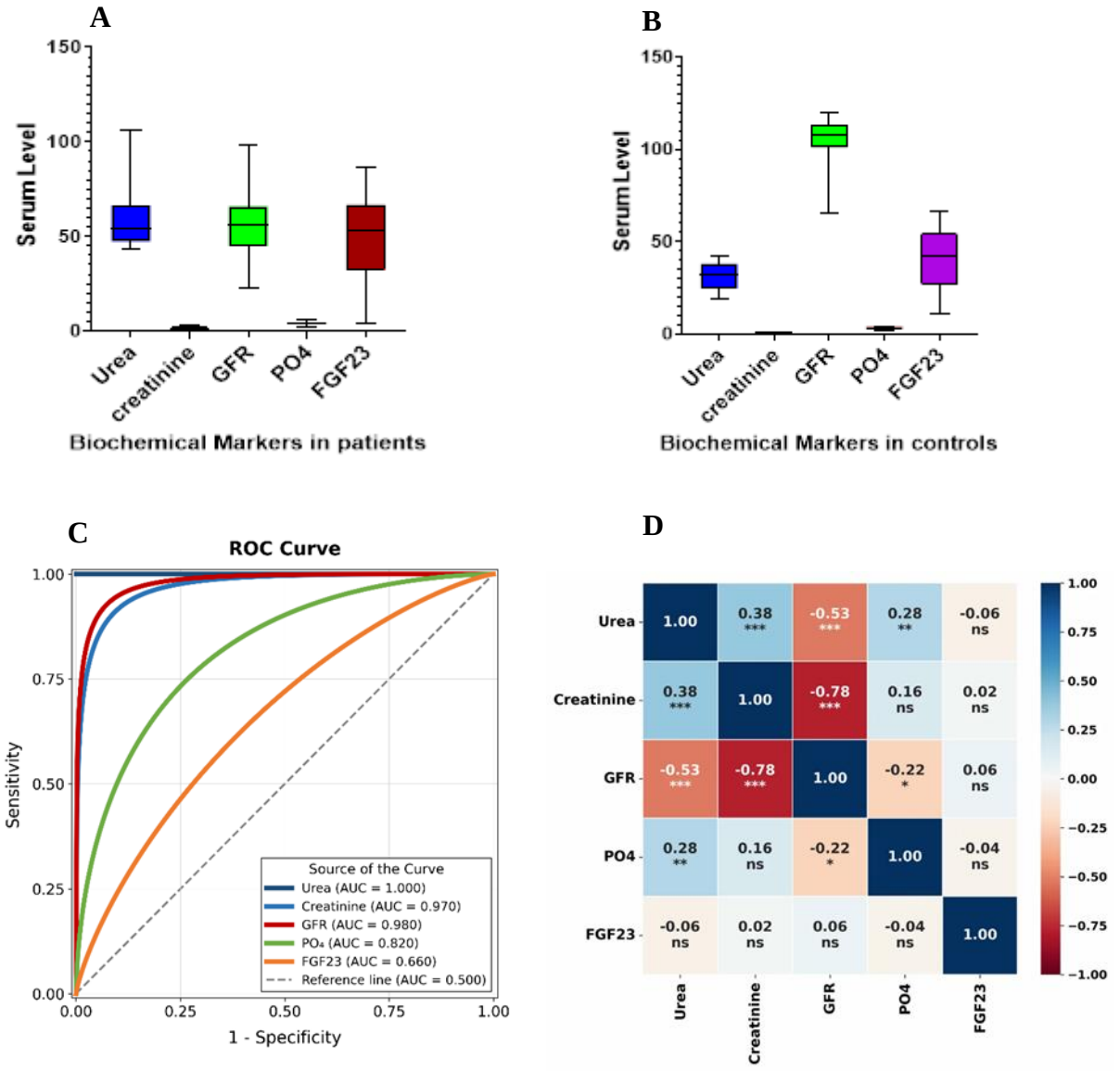

Figure1: Comparison of The Biochemical and Hormonal Data of Renal Dysfunction Markers in The Patient and Control Cohorts. (A) Box plots for the patient cohort data of serum urea, creatinine, GFR, PO_4, and FGF23. (B) Control cohort data for the same parameters shown with corresponding box plots. (C) Receiver Operating Characteristic (ROC) curves for the patient and control cohort markers that best differentiated the cohorts; urea and creatinine had the greatest discriminatory power, (AUC = 1.000 and 0.970 respectively), then GFR (AUC = 0.980, reverse direction), PO_4 (AUC = 0.820), and FGF23 (AUC = 0.660). (D) The Spearman's correlation matric of the five parameters in the patient cohort; the different colors denote the correlation (blue = positive, red = negative). The asterisks indicate the level of significance (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$); ns = non-significant.

4. Discussion

The study indicated that FGF23 could more clinically positive and biochemically constructive approach at the very first stages of renal impairment by treating FGF23 as a primary hormonal factor. The significant age of the patient cohort corresponds with the well-established epidemiological and physiological association of age and progressive nephron senescence with measurable declines in glomerular filtration that has been documented in varying ethnic groups (Grabner *et al.*, 2015) The patient cohorts biochemical profile exhibiting both significantly high serum urea, creatinine, and phosphate and considerably low estimated GFR which remains consistent with study established biochemical effects of early nephron loss and reduced tubular secretory capacity (Hu *et al.*, 2015) A compatible study was performed with CKD patients and also reported significantly high urea, creatinine, and phosphate and low GFR [13]. In addition, another study confirmed that in CKD patients, even if phosphate levels are elevated but remain at or near the upper reference limit, it indicates early failure of the tubular phosphate secretory mechanism when there is no failure in the system and clinically apparent thresholds, representing the phase that more sensitive hormonal biomarkers are aimed to capture (Wolf *et al.*, 2016; Sriperumbuduri *et al.*, 2020) The statistically significant increase of circulating FGF23 in the study cohort, which is in accordance with the emerging paradigm of the early compensatory increase of FGF23 in CKD and before the development of overt hyperphosphatemia and the metabolic imbalances (Isakova *et al.*, 2018) Another study that corroborated the findings of the current study was done on subjects with early nephropathy, which reported significantly increased levels of circulating FGF23 in comparison to their paired controls, even in subjects with biochemically normal levels of phosphatemia, therefore indicating an early compensatory phosphaturic hormonal response to incipient tubular phosphate retention sub clinically (Levin *et al.*, 2017) Study demonstrated that the increase FGF23 levels in CKD phase occurs much before the increase of the there is a marked increase in parathyroid hormone, serum phosphate, and creatinine levels, indicating that FGF23 is the first of the CKD endocrine disorders (Scialla and Wolf, 2014) The slight increase of FGF23 observed in the present cohort is statistically significant but is much lower than the expected strong increase in FGF23 in advanced stages of CKD, which indicates an early adaptive response. . This early adaptive response indicates that the FGF23 levels are adjusting to the level of sub clinically retained tubular phosphate, and there is no receptor level resistance that would move the compensatory response to a pathological level of hormonal dysregulation (Raju and Saxena, 2025) The analysis of the diagnostic performance provides a clinically useful and informative description of biomarker discriminatory performance. (Laville *et al.*, 2023) Although phosphate is discriminatory and excellent, it is still less so than the filtration markers, but it provides reason to indicate that it is a sensitive, early marker of tubular performance impairment with respect to mineral management. Levin and colleagues reported a study that demonstrated that phosphate abnormalities in CKD patients were revealed at GFR levels that were significantly greater than those levels at which creatinine-based staging identified the disease, thus positioning phosphate as a useful biomarker in the early detection of renal dysfunction (Fang *et al.*, 2020) Of the discriminatory performances of the FGF23 that are moderate, statistically significant, but markedly lower than the traditional biochemical ones, it is completely consistent with its pathophysiological role, which is that of a hormonal early warning system working upstream of the biochemical changes that it is intended to prevent. A study supporting this position, pointing out that the clinical utility of FGF23 is not in its either/or diagnostic potential, but rather in its differentiation of hormonal risk and forecasting of negative renal outcomes, even at a stage where standard biochemical metrics are optimistically normal (Bikbov *et al.*, 2020) This suggests that FGF23 should function primarily as a hormonal supplement in a multi-marker diagnostic approach, rather than as a sole diagnostic biomarker, a differentiation that holds substantial practical value in positioning FGF23 for meaningful use in early renal practice. The lack of statistically significant correlations between circulating FGF23 and individual biomarkers of glomerular filtration and

phosphate metabolism in the present patient cohort is of considerable mechanistic interpretive value (Komaba and Fukagawa, 2012) The apparent disconnection between FGF23 levels and standard biochemical markers in the early stages of renal impairment is consistent with the FGF23 hypothesis as an upstream hormonal mediator, whose levels are influenced by integrated skeletal and tubular phosphate sensing mechanisms that are not captured in a linear fashion by any individual biochemical marker (Hu, Kuro-O and Moe, no date) Wolf's study is consistent with this hypothesis; he showed that in early CKD the relationship between FGF23 and serum phosphate is understood to be non-linear and contextual, with the two variables becoming decoupled during the compensatory phase when FGF23 is able to maintain phosphate equilibrium despite its progressive increase (Martín-Vírgala *et al.*, 2024) In addition, the absence of a considerable FGF23–GFR relationship at this early stage of the disease is in contrast to the classical and well-established presence of a strong inverse relationship in advanced CKD, which suggests that the current cohort's glomerular filtration rate (GFR) deficit has not yet reached a level where FGF23 accumulation becomes its predominant determinant, which will occur at more advanced levels of nephron loss (Donate-Correa *et al.*, 2024) The absence of an inverse relationship between FGF23 and its biochemical parameters is an early indicator that there are later stages of CKD where FGF23 is not a biochemical signal that correlates with the status of the disease. There are numerous clinical and translational implications resulting from these findings. Identifying FGF23 levels during early renal dysfunction and understanding where FGF23 levels are mildly elevated and not yet complex with receptor resistance, allows us to define a clinical opportunity and therapeutic window. Most nephroprotective interventions aimed at restoring hormonal balance and averting downstream FGF23-related organ toxicity, are expected to be effective when implemented early and within the range of the FGF23 hormonal shift before the complete FGF23-Klotho receptor uncoupling of advanced CKD. Examples of these interventions are dietary phosphate restriction and phosphate binders. A study supporting this therapeutic rationale showed that early nephroprotective interventions based on FGF23 levels, significantly reduced the rate of GFR decline. This provided the first direct evidence that FGF23 driven management, translated to relevant renal outcome (Gutiérrez *et al.*, 2008; Gutiérrez, 2013; Stevens *et al.*, 2024)

Conclusion

Initial stages of renal dysfunction exhibit compensatory secretion of circulating FGF23 accompanied by biochemical markers demonstrating glomerular filtration failure and tubular dysregulation of phosphate. FGF23, although having only moderate diagnostic performance, is considered to be an early hormonal signal before traditional biochemical perturbations occur. This phenomenon advocates FGF23 combination with standard renal biomarkers to improve the early identification and accurate classification of renal impairment.

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