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The prognostic and diagnostic value of fibroblast growth factor 23 in patients undergoing hemodialysis

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Abstract. *Fibroblast growth factor 23 (FGF23) is a phosphotropic hormone secreted by osteoblasts and osteocytes into the systemic circulation. It exerts its effects on the kidneys, parathyroid glands, heart, and bones. FGF23 is a critical phosphaturic hormone that, alongside parathyroid hormone (PTH), regulates phosphate reabsorption and calcitriol ($1,25(OH)_2D$) synthesis in the kidneys. The present study aimed to evaluate the diagnostic and prognostic significance of fibroblast growth factor 23 in patients undergoing hemodialysis.*

Methods. A total of 88 patients were examined in this cross-sectional study. The cohort comprised 36 women (40.9%; 95% CI 30.64–51.18) and 52 men (59.1%; 95% CI 48.82–69.36), with a mean age of 55.81 ± 13.14 years. Group 1 consisted of 69 patients with stage 5 chronic kidney disease (CKD) receiving renal replacement therapy via hemodialysis, while Group 2 included 19 patients with stage 3 CKD.

Results. FGF23 levels were elevated in 67 patients (97.1%; 95% CI 91.87–99.72) in Group 1, with a median (Me) of 1258.32 pg/mL (interquartile range [IQR] 169.46–1338.46). In Group 2, FGF23 levels were elevated in 18 patients (94.7%; 95% CI 80.58–100), with a median of 150.5 pg/mL (IQR 74.22–929.12). A significant difference was observed between the groups ($p < 0.05$). The median duration of hemodialysis in Group 1 was 15 months (IQR 8–36). In Group 1, correlation analysis revealed weak associations between FGF23 and phosphorus ($r = 0.13$; $p > 0.05$), total calcium ($r = 0.04$; $p < 0.05$), ionized calcium ($r = 0.02$; $p < 0.05$), and parathyroid hormone ($r = 0.08$; $p > 0.05$). Significant correlations were found between FGF23 and creatinine ($r = 0.41$; $p < 0.005$), urea ($r = 0.33$; $p < 0.005$), urine volume ($r = -0.75$; $p < 0.005$), and hemodialysis duration ($r = 0.57$; $p < 0.005$). Regression analysis for predicting residual urine volume based on FGF23, creatinine, urea, and hemodialysis duration yielded an R^2 of 0.7369, F-statistic of 92.45 ($p < 0.0001$), standard error of residuals of 5.843, and residual degrees of freedom of 66.

Conclusions. The weak correlations between FGF23 and calcium-phosphorus metabolism indicate that FGF23 is not a suitable diagnostic marker for mineral and bone disorders (CKD-MBD) in patients undergoing hemodialysis. However, FGF23 is a significant predictor of residual urine volume in hemodialysis patients, as demonstrated by the regression analysis. The model, incorporating FGF23 and hemodialysis duration, explains 73.7% of the variation in urine volume, highlighting its strong prognostic capability. These findings underscore the clinical significance of FGF23 as a biomarker for assessing residual renal function in dialysis patients.

Keywords: *fibroblast growth factor 23, chronic kidney disease, hemodialysis, calcium-phosphate metabolism, diuresis.*

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Прогностична та діагностична значимість фактора росту фібробластів 23 у пацієнтів, які лікуються методом гемодіалізу

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Резюме. *Фактор росту фібробластів 23 (ФРФ23) є фосфотропним гормоном. Він секретується остеобластами та остеоцитами в системний кровообіг і реалізує свій вплив у нирках, паращитовидних залозах, серці та кістках. ФРФ23 є критичним фосфатуричним гормоном, який, разом з паратиреоїдним гормоном (ПТГ), регулює рециркуляцію фосфатів та синтез кальцитріолу (1,25(OH)2D) в нирках. Метою цієї роботи було встановити діагностичну та прогностичну значимість фактора росту фібробластів 23 у пацієнтів, які лікуються гемодіалізом.*

Методи. До цього одномоментного дослідження було залучено 88 пацієнтів. Серед обстежених хворих було 36 (40.9%; 95% ДІ 30.64-51.18) жінок та 52 (59.09%; 95% ДІ 48.82-69.36) чоловіків, середній вік – 55.81±13.14 років. 1 групу склали 69 пацієнтів з ХХН 5 стадії, які знаходяться на замісній нирковій терапії методом гемодіалізу, 2 групу 19 пацієнтів з ХХН 3ст.

Результати. Рівні ФРФ23 були підвищені у 67 (97.1%; 95% ДІ 91.87-99.72) в 1 групі Me 1258.32 (169.46; 1338.46) пг/мл, у той час у групі 2 рівень ФРФ23 був вище норми у 18 хворих (94.74%; 95% ДІ 80.58-100) Me 150.5 (74.22; 929.12). Було виявлено достовірну різницю між групами ($p<0.05$). Тривалість проведення гемодіалізу становила (місяцях) Me 15 (8; 36). В 1 групі було проведено кореляційний аналіз між ФРФ23 та фосфором($r=0.13$; $p>0,05$), Са (заг)($r=0.04$; $p<0.05$), Са (іон)($r=0.02$; $p<0.05$), паратгормоном($r=0.08$; $p>0.05$). Також в 1 групі встановлено кореляційні зв'язки між ФРФ23 та креатиніном($r=0.41$; $p<0.005$), сечовиною($r=0.33$; $p<0.005$), об'ємом діурезу($r=-0.75$; $p<0.005$), тривалістю гемодіалізу($r=0.57$; $p<0.005$). Результати регресійного аналізу для прогнозування кількості залишкового діурезу в залежності від ФРФ23, креатиніну, сечовини, тривалості гемодіалізу: $R^2=0.7369$. F-статистика: 92.45 ($p<0.0001$). Стандартна помилка залишків: 5.843. Ступені свободи залишків: 66.

Висновки. Слабкі кореляції ФРФ23 з кальцієво-фосфорним обміном роблять його непридатним діагностичним маркером порушень КФО у пацієнтів на програмному гемодіалізі. ФРФ23 є значущим предиктором об'єму діурезу у пацієнтів на гемодіалізі згідно з результатами регресійного аналізу. Модель, яка включає ФРФ23 та тривалість гемодіалізу, пояснює 73.7% варіації діурезу, що свідчить про її високу прогностичну здатність. Це підкреслює клінічну значимість ФРФ23 як біомаркера для оцінки залишкової функції нирок у пацієнтів на діалізі.

Ключові слова. *Фактор росту фібробластів 23, хронічна хвороба нирок, гемодіаліз, кальцієво-фосфорний обмін, діурез.*

Introduction. Fibroblast growth factor 23 (FGF23) is a phosphotropic hormone. It is secreted by osteoblasts and osteocytes into the systemic circulation and exerts its effects on the kidneys, parathyroid glands, heart, and bones. FGF23 is a critical phosphaturic hormone that, along with parathyroid hormone (PTH), regulates phosphate recirculation and calcitriol (1,25(OH)2D) synthesis in the kidneys [1]. In the parathyroid gland and kidneys, FGF23 suppresses PTH secretion and reduces the production of active vitamin D. By acting on the epithelial cells of the proximal tubules, FGF23 reduces the surface expression of sodium/phosphate cotransporters, thereby decreasing renal phosphate reabsorption. The cumulative physiological effect of FGF23 is to increase renal phosphate excretion and decrease systemic phosphate levels. However, in chronic kidney disease (CKD), phosphate excretion and the renal effects of FGF23 are reduced due to the loss of functional renal mass and decreased α-Klotho expression, leading to high serum phosphate and FGF23 levels. Starting from the early stages of CKD, serum FGF23 levels progressively increase to maintain normal phosphate levels, but cannot promote renal phosphate excretion as nephron function and sensitivity to FGF23 decrease. In patients with end-stage renal disease (ESRD) who are dependent on renal replacement therapy, FGF23 levels can reach 1000 times the normal range. Elevated FGF23 levels are associated with various pathological conditions, including secondary hyperparathyroidism, osteoporosis, cardiac remodeling, and increased risk of cardiovascular mortality in CKD patients [2].

FGF23 contributes to maintaining phosphate, calcium, 1,25(OH)2D, and PTH homeostasis. Additionally, factors such as iron deficiency, erythropoietin, and inflammation play a significant role in FGF23 synthesis and degradation [3].

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In patients with CKD, a strong association is observed between elevated FGF23 levels and an increased risk and progression of vascular calcification [4]. FGF23 is considered a potential prognostic biomarker for vascular calcification and cardiovascular events in this population [5]. The consistent correlation between high FGF23 levels and the risk of vascular calcification in CKD underscores the need to understand the underlying mechanisms in this high-risk group.

Currently, the use of FGF23 for assessing calcium-phosphate metabolism in hemodialysis patients is not standard practice due to methodological limitations. The lack of standardized measurement methods and established reference values significantly complicates the interpretation of FGF23 levels. Furthermore, the utility of FGF23 for assessing residual kidney function in this patient category remains insufficiently studied and warrants further investigation. Therefore, the present study aimed to determine the diagnostic and prognostic significance of fibroblast growth factor-23 in patients undergoing hemodialysis.

Materials and Methods. This cross-sectional study involved 88 patients with chronic kidney disease (CKD), including 69 patients with stage 5 CKD undergoing renal replacement therapy with hemodialysis (Group 1). A comparison group of 19 hospitalized patients with stage 3 CKD was also selected (Group 2). The study was conducted in accordance with international standards regarding the coordinated participation of respondents, the ethical component of research, and the collection of biomaterial (Helsinki Declaration of the World Medical Association – «Ethical Principles for Medical Research Involving Human Subjects» and «Universal Declaration on Bioethics and Human Rights» (UNESCO)). The study protocol was approved by the local ethics committee of Danylo Halytsky Lviv National Medical University (protocol number 3 dated March 18, 2024). All patients signed a written informed consent to participate in the study.

Among the examined patients, there were 36 (40.9%; 95% CI 30.64-51.18) women and 52 (59.09%; 95% CI 48.82-69.36) men, with mean age 55.81±13.14 years. The inclusion criteria for patients in the study were: being on renal replacement therapy with hemodialysis for at least 6 months, age from 18 to 85 years, patient consent to participate in the study, and ability to adequately cooperate during the study. Exclusion criteria: patient refusal to participate in the study, age <18 years, information about acute infectious processes of any etiology, oncological diseases, and mental disorders.

In all patients, the diagnosis of CKD was established in accordance with the order of the Ministry of Health of Ukraine No. 593 dated 02.12.2004 (as amended by the order of the Ministry of Health of Ukraine No. 384 dated 24.05.2012) [6] and according to the recommendations of the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2024 [7].

All patients underwent a standard examination, which included general clinical, biochemical, and instrumental methods of examination. Biochemical parameters were determined in the laboratory of St. Panteleimon Hospital 1TMU in Lviv. The glomerular filtration rate (GFR) was calculated using the CKD-EPI (2021) formula to identify and select individuals with stage 3 chronic kidney disease (CKD) for the comparison group. PTH and FGF23 levels were determined by enzyme-linked immunosorbent assay (ELISA). To determine FGF23, a reagent kit from FineTest (China) was used. Reference values were 0-25 pg/mL for healthy serum. The assay demonstrated a sensitivity of 9.375 pg/mL, indicating its capacity to detect low concentrations of FGF23. The specificity of the assay was confirmed by its ability to specifically recognize FGF23, with no observed cross-reactivity with other analogous molecules. This high specificity ensures the accurate quantification of FGF23 without interference from related substances.

The «RStudio» program was used to calculate statistical indicators. General statistical indicators were calculated in «Microsoft Excel» using built-in formulas. The frequency of qualitative indicators was presented as absolute (n) and relative (%) values, as well as a 95% confidence interval (CI) in the form «n (%; 95% CI)». When analyzing quantitative data, the distribution of values was determined using the Shapiro-Wilk test. For quantitative data with a normal distribution, the results were presented as mean and standard deviation (M±SD). For quantitative data with a non-normal distribution, the median and 25-75 quartiles (Me (Q25-Q75)) were used. To compare two independent samples, the non-parametric Mann-Whitney U test was used. Spearman's rank correlation coefficient was used to analyze the correlation between quantitative indicators. The backward stepwise regression method was used to determine the prognostic significance. The statistical significance of the correlation coefficients was established. The critical significance level (p) for testing statistical hypotheses in this study was set at 0.05.

Results. The results of the study yielded the following data. FGF23 levels were elevated in 67 (97.1%; 95% CI 91.87-99.72) patients in Group 1, with a median (Me) of 1258.32 (169.46; 1338.46) pg/mL, while in Group 2, FGF23 levels were above normal in 18 patients (94.74%; 95% CI 80.58-100), with a Me of 150.5 (74.22; 929.12). A significant difference was found between the groups ($p<0.05$).

Since the primary function of FGF23 is to maintain phosphate, calcium, and parathyroid hormone metabolism, all patients underwent an assessment of calcium-phosphate metabolism (CPM) parameters. To determine renal excretory function, creatinine and urea levels, as well as urine output, were analyzed (Table 1).

Table 1

CPM and Renal Function Parameters in CKD Patients

Parameter	Group 1	Group 2	p
Phosphorus, mmol/L	1.61 (1.22; 2.11)	1.06 (0.87; 1.17)	<0.0001
Total Calcium, mmol/L	2.6 (2.44; 2.78)	2.37 (2.27; 2.45)	<0.0001
Ionized Calcium, mmol/L	1.31 (1.2; 1.39)	1.17 (1.13; 1.24)	0.0001
Parathyroid Hormone, pg/mL	201 (118; 314)	56 (44; 133)	0.0001
Creatinine, µmol/L	783 (540; 971)	158 (150; 169)	<0.0001
Urea, mmol/L	22.6 (18.8; 27.4)	11.1 (10; 11.95)	<0.0001
Diuresis, mL/kg/day	9.1 (2.6; 20.77)	30.6 (28.3; 33.85)	<0.0001

The duration of hemodialysis was (in months) Me 15 (8; 36). To assess the effect of FGF23 on CPM in Group 1, a correlation analysis was performed between FGF23 and phosphorus (r=0.13; p>0.05), total Ca (r=0.04; p<0.05), ionized Ca (r=0.02; p<0.05), and parathyroid hormone (r=0.08; p>0.05). Post-hoc power analysis for the non-significant correlations indicated insufficient power (power = 0.1892 for phosphorus; power = 0.1101 for PTH). The estimated sample sizes required to detect such weak associations with 80% power at an alpha of 0.05 were 456 and 1027 observations, respectively.

Further, to clarify the effect of FGF23 on renal excretory function, a correlation analysis was performed between FGF23 and creatinine, urea, urine output, and hemodialysis duration in Group 1 (Fig. 1-4).

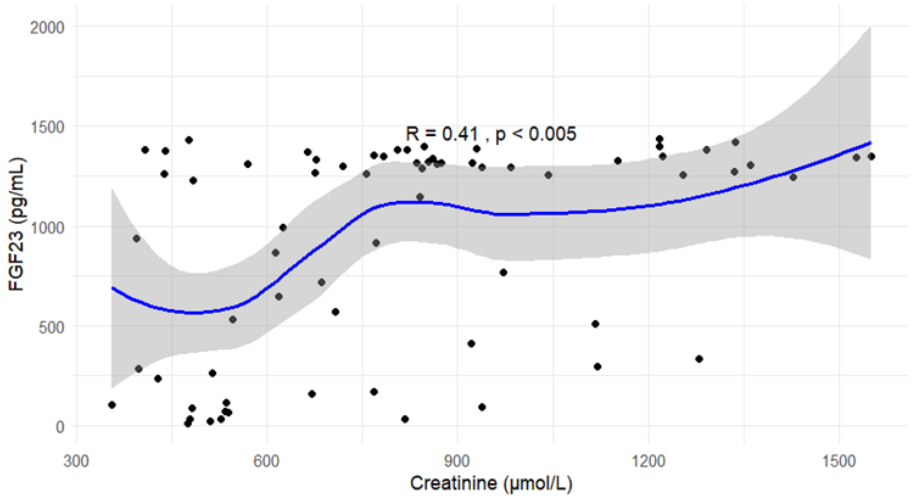

Fig. 1. Correlation between FGF23 and creatinine levels.

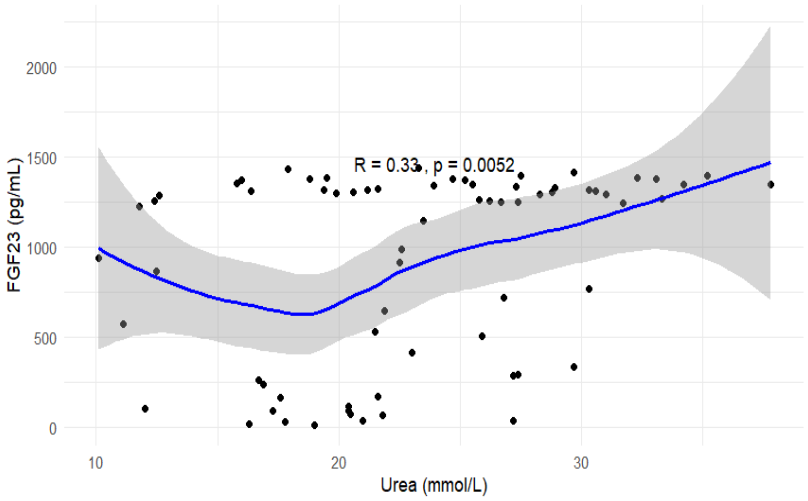

Fig. 2. Correlation between FGF23 and urea levels.

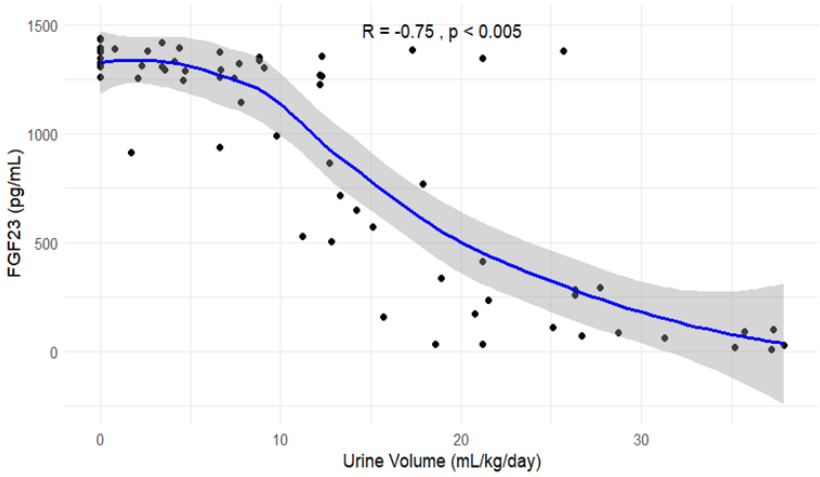

Fig. 3. Correlation between FGF23 and urine volume levels

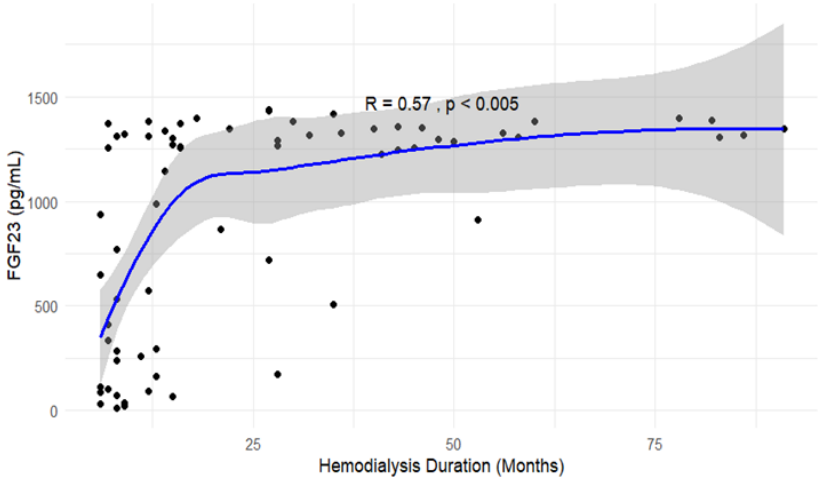

Fig. 4. Correlation between FGF23 levels and hemodialysis treatment duration.

Subsequently, a backward stepwise multiple linear regression analysis was conducted to develop a model predicting urine output (mL/kg/day) using initial candidate predictors: FGF23, creatinine, urea, and hemodialysis duration. The final model, after the removal of non-significant predictors (creatinine, p=0.7991; urea, p=0.9156), included FGF23 and hemodialysis duration (Table 2).

Table 2

Final Model from Backward Stepwise Regression Predicting Urine Output

Variable	Estimate	Standard Error	t-value	P-value
(Intercept)	29.306665	1.436711	20.398	<0.0001
FGF23	-0.015690	0.001562	-10.044	<0.0001
Dialysis Duration	-0.101998	0.036838	-2.769	0.0073

R2=0.7369, indicating that the model can predict 73.7% of urine output variations. F-statistic: 92.45 tests the overall significance of the model. The p-value of the F-statistic is <0.0001, indicating that the model is statistically significant. Residual standard error: 5.843. Residual degrees of freedom: 66. From these data, we can draw the following conclusions:

1. The model is statistically significant for predicting urine output.
2. FGF23 has a significant negative impact on urine output.
3. The amount of time on dialysis has a significant impact on urine output.
4. Creatinine and urea do not have a significant impact on urine output, so they were excluded from the model.
5. The model explains 73.7% of the variance in urine output. Thus, we can conclude that the model is adequate for explaining the influence of FGF23 and dialysis duration on urine output (Fig. 5, 6).

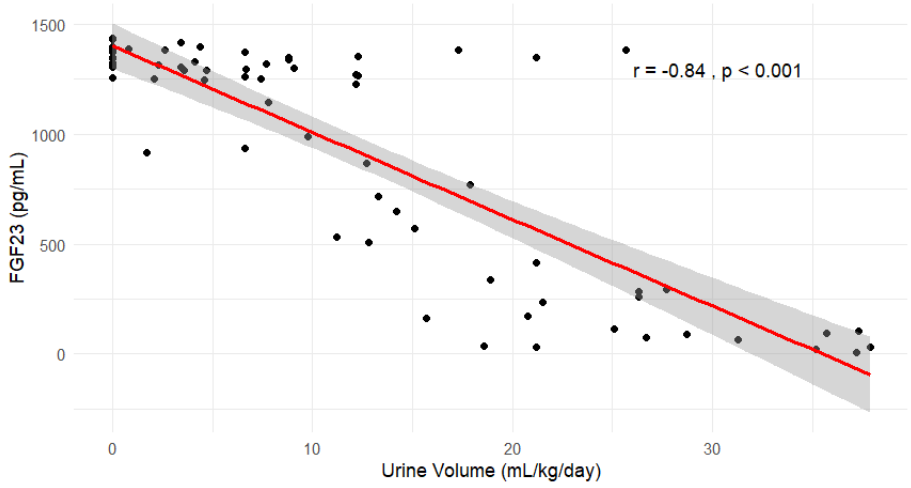

Fig. 5. Effect of FGF23 on urine output.

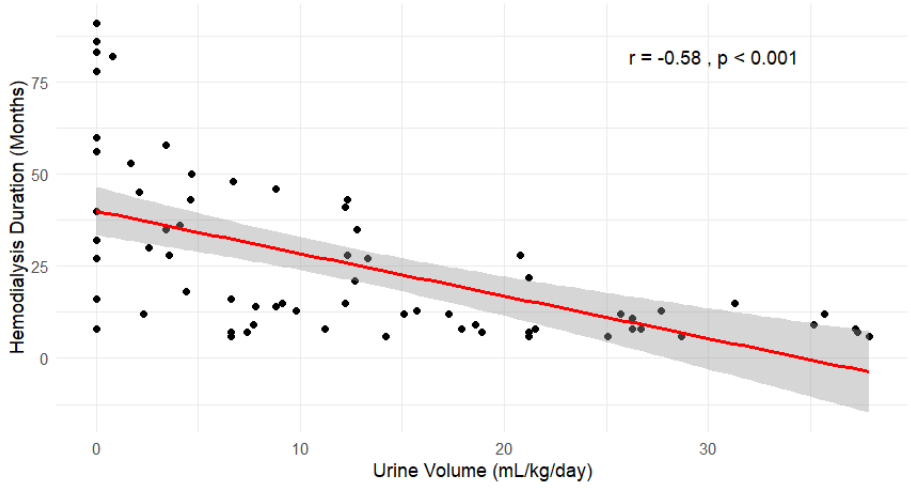

Fig. 6. Effect of hemodialysis duration on urine output.

Discussion. Fibroblast growth factor 23 is a key hormone in the regulation of phosphate homeostasis. Over the past decades, FGF23 has been the subject of intensive research in nephrology and cardiology. The uniqueness of FGF23 lies in its early appearance at the preclinical stages of CKD. In a study by Fauconnier C., the authors report high sensitivity and specificity of the FGF23 assay for the diagnosis of mild to moderate CKD, compared to the use of eGFR and creatinine [10]. Some scientific papers show that FGF23 can be a marker of hypophosphatemia [8], while others point to its potential as an early marker of calcium-phosphorus disturbances in the early stages of CKD [9]. In a Chinese study, the authors show that FGF23 can be a marker of vascular calcification, especially in stage 5 renal failure. They state that eGFR, serum creatinine, and FGF23 are independent risk factors for heart valve calcification in patients with CKD [11].

Our findings in patients undergoing maintenance hemodialysis, however, revealed no significant associations between FGF23 and phosphorus or parathyroid hormone, and only very weak significant associations with total and ionized calcium. These results suggest that FGF23 may not be a reliable diagnostic marker for assessing ongoing mineral metabolism disturbances in this specific patient population. Interpreting FGF23 levels is further complicated by its dual role reflecting not only mineral metabolism but also the degree of residual renal function (RRF). This dual role should be considered.

While literature supports FGF23's utility in early CKD or for vascular calcification risk assessment, our results do not confirm its diagnostic effectiveness for routine CPM monitoring in maintenance hemodialysis patients. Conversely, consistent with studies highlighting FGF23's potential for assessing renal function [12, 13], possibly with advantages over eGFR in certain contexts, our study found strong associations related to RRF.

We observed a strong, statistically significant negative correlation between FGF23 concentration and urine output (an indicator of RRF). This underscores the potential value of FGF23 as a biomarker reflecting RRF in patients with advanced kidney disease.

The interpretation of this negative association (higher FGF23, lower urine output) involves complex physiology. Potential mechanisms contributing to lower urine output with higher FGF23 could include direct hormonal effects, such as suggested activation of the

renin-angiotensin-aldosterone system (RAAS) [17] or upregulation of the Na-Cl cotransporter (NCC) [18], both promoting sodium and water retention. Alternatively, and perhaps more likely in this population, the markedly elevated FGF23 levels primarily serve as a sensitive marker of the severity of underlying renal dysfunction and loss of nephron mass, which is the principal determinant of reduced urine output. The phosphaturic effect of FGF23 [15], while physiologically important, is unlikely to be the dominant factor driving the negative correlation with overall urine volume observed in our stage 5 CKD cohort.

Further complicating the picture are these potential non-phosphaturic effects of FGF23. Evidence suggests possible activation of the RAAS [17] and regulation of NCC expression in the distal tubules [18], both of which typically lead to sodium and water retention (an antidiuretic effect) and increased blood pressure. While seemingly counterintuitive given FGF23's primary phosphaturic role [19], these fluid-retaining mechanisms [17] could potentially contribute to, rather than contrast with, the observed overall negative association between markedly elevated FGF23 levels and reduced urine output in our cohort with severe renal failure. This highlights the complex, multifactorial influence of FGF23 on water and salt balance in CKD, where its role extends beyond phosphate regulation and likely reflects the profound loss of renal function.

We also observed increased FGF23 levels with a longer duration of dialysis treatment, although this correlation was less significant for predicting urine output. This aligns with literature data indicating a progressive decline in residual renal function in patients on chronic dialysis [19]. Decreased RRF leads to impaired phosphate excretion and the development of hyperphosphatemia, which is a potent stimulus for compensatory FGF23 hypersecretion by osteocytes [20]. Therefore, high FGF23 levels in patients with a long history of dialysis primarily reflect the loss of RRF and the body's attempt to maintain phosphate homeostasis [20]. This explains why FGF23 level, rather than dialysis duration, correlates more closely with urine output as an indicator of preserved renal function.

The results of the regression analysis demonstrate that FGF23 is a significant predictor of changes in urine output in patients on hemodialysis, surpassing traditional markers such as creatinine and urea in its predictive value. Backward stepwise regression analysis revealed a statistically significant negative correlation between FGF23 levels and urine output, confirming the hypothesis of its effect on renal excretory function. The model, which includes FGF23 and hemodialysis duration, explains 73.7% of the variation in urine output, indicating its high predictive ability. This underscores the clinical significance of FGF23 as a biomarker for assessing residual renal function in dialysis patients. When interpreting the regression analysis model, it is necessary to note factors that were not included in the model but could potentially influence its results. These factors include: the etiology CKD, patient age, the presence and severity of comorbidities (especially cardiovascular disease), dialysis therapy parameters other than duration (specifically, modality [HD/HDF], and the ultrafiltration strategy and rate, which affect intradialytic hemodynamics), individual fluid and sodium intake, nutritional status, the degree of systemic inflammation, as well as the use of certain medications, particularly diuretics or renin-angiotensin system inhibitors. Potentially accounting for these factors could enhance the model's predictive performance.

We found a negative correlation between hemodialysis duration and urine output, which is consistent with known data on the progressive decline in residual renal function in patients on long-term dialysis [14]. The lack of significant correlation between urine output and creatinine and urea may be due to limitations of these markers in assessing residual renal function, especially in dialysis patients, but this issue requires further study. A deeper understanding of the role of FGF23 in the pathogenesis of CKD and calcium-phosphorus disorders should expand the clinical indications for its use as a diagnostic and prognostic marker and identify new therapeutic targets for the treatment of CKD and heart failure.

Limitations. Firstly, the cross-sectional design precludes establishing causality or tracking changes over time. Secondly, the sample size provided insufficient statistical power to definitively assess correlations between FGF23 and phosphorus/PTH, limiting conclusions about FGF23's diagnostic role for specific CPM parameters in this group, despite non-significant findings. Thirdly, focusing on stage 5 CKD patients on maintenance hemodialysis limits the generalizability of findings, particularly regarding FGF23 and RRF assessment, to patients with earlier CKD stages or on different RRT modalities. Fourthly, the regression model did not include several potential confounders, which could influence the observed associations.

Conclusions:

1. FGF23 is unsuitable as a diagnostic marker for calcium-phosphorus disorders in patients undergoing programmed hemodialysis, not only because of its weak correlations with calcium-phosphorus metabolism parameters but also due to its strong negative correlation with residual kidney function.
2. FGF23 is a significant predictor of urine output in hemodialysis patients according to the results of the regression analysis.
3. The model, which includes FGF23 and hemodialysis duration, explains 73.7% of the variation in urine output, indicating its high predictive ability. This underscores the clinical significance of FGF23 as a biomarker for assessing residual renal function in dialysis patients. A model integrating these parameters shows promise as a tool for identifying patients with lower residual urine output, reflecting reduced RRF among those on maintenance hemodialysis.

Future research should focus on elucidating the mechanisms behind the strong negative association between FGF23 and residual diuresis in hemodialysis patients. Investigating the impact of different therapeutic interventions on FGF23 levels and subsequent preservation of RRF is warranted. Additionally, developing standardized FGF23 assays remains crucial for facilitating its broader clinical application.

Ethical declaration: The research protocol was reviewed and approved at the meeting of the Commission on Ethics of Scientific Research, Experimental Development, and Scientific Works of Danylo Halytsky Lviv National Medical University on March 18, 2024, protocol number 3. Written informed consent was provided to patients for participation in the study.

Conflict of interest statement: The authors declare no conflict of interest.

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Author contributions

Bardash V.O.: conceptualization and design, data collection, statistical analysis.

Maksymets T.A.: writing and interpretation

Skliarov E.Ya.: review and editing.

Data Availability: The data analyzed in the study can be provided upon reasonable request.

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