REVIEW

By Prof. Atanas Ivanov Kundurdzhiev, DM , Ph.D
Head of the Nephrology Clinic at UMHAT "St. Ivan Rilski"
Elected as a member of the scientific jury by Order № 15-05-169/11.08.2025
of the Executive Director and Procurator of UMHAT "Acibadem City Clinic Tokuda Hospital"
for the public defense procedure of the dissertation of
Dr. Dilyana Mihaylova Nikolova
for awarding the educational and scientific degree "Doctor"
on the topic:
THE ROLE OF FIBROBLAST GROWTH FACTOR 23 IN THE DEVELOPMENT OF RENAL BONE DISEASE AND CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH CHRONIC KIDNEY DISEASE
Acibadem City Clinic Tokuda Hospital
Scientific supervisor: Assoc. Prof. Aleksandar Osichenko, DM

1   Biographical data:

Dr. Dilyana Nikolova graduated in medicine in 1996 with very good success and began working at the 5th City Hospital in the Internal Medicine Clinic. From 2005 to 2012, she was an assistant at the Clinic of Nephrology and Transplantation at UMHAT Aleksandrovska, and since 2012 she has worked as a nephrologist in the Nephrology Department of the Internal Medicine Clinic at Acibadem City Clinic Tokuda Hospital to the present. Since December 2022, she has been the Head of the Nephrology Department. She obtained her Internal Medicine specialty in 2005 and her Nephrology specialty in 2012. In 2024 she received a Master's Diploma in Public Health and Health Management from the Medical University of Sofia. Dr. Nikolova is proficient in all basic methods of diagnosis and treatment in nephrology.

2   Evaluation of the relevance of the topic, structure, and results:

Chronic kidney disease (CKD) is widespread and often asymptomatic. Screening, early diagnosis, and prognosis determination are key to successful treatment.

In 2006, KDIGO introduced the term CKD-MBD (Chronic Kidney Disease – Mineral and Bone Disorder). This is a new concept for the role of calcium-phosphate metabolism, not only for increased fracture risk but also for vascular damage, left ventricular hypertrophy, and other disorders such as neurodegenerative diseases, cognitive impairment, and hematopoiesis suppression. Central to this concept are hyperphosphatemia and the associated increase in Fibroblast Growth Factor 23 (FGF-23).

In this dissertation, Dr. Nikolova aims to study the role of the laboratory marker FGF-23 in the diagnosis and treatment of renal bone disease and cardiovascular complications in CKD patients. Establishing a biomarker in clinical practice is a long and complex process. It must be proven precise, reproducible, non-duplicative of other information, patient-acceptable, easy to interpret, highly sensitive and specific, and, importantly, accessible.

The dissertation is 106 standard pages and classically structured. It includes 36 figures and 9 tables, all well-illustrated graphically, making the work well visualized. It is written in standard literary Bulgarian. The literature review spans 27 pages, contains 16 chapters, and ends with conclusions, which directly lead to the aim and objectives. These are properly

formulated: to determine the place and role of FGF-23 testing in the diagnostic-therapeutic process in CKD patients. The "Materials and Methods" section describes in detail the validated and standardized methods of laboratory and clinical investigations used. A total of 103 patients were studied—58 men and 45 women—a sufficient number to accomplish the tasks.

The results are presented clearly on 23 pages. The statistical processing and derived patterns are impressive. Logistic regression was conducted to assess the effect of eGFR, phosphorus, and PTH on FGF-23 levels. It was shown that an increase of one unit in eGFR reduces the chances of PTH being above normal by 5.1%, with changes in PTH values tracked across CKD stages. Similarly, changes in FGF-23 values were tracked, as well as the relationship between elevated FGF-23 and phosphorus levels. Of interest is the investigation of variations in PTH and FGF-23 values among patients with identical eGFR who receive calcitriol versus those who do not, as this has implications for therapeutic decisions.

The search for associations between major cardiovascular events and PTH and FGF-23 values is particularly relevant. Logistic regression revealed no statistically significant effect of FGF-23 on the presence of cardiovascular events (myocardial infarction or stroke) but did find a statistically significant effect of PTH, albeit with a very low coefficient.

These data identify FGF-23 as an important laboratory marker in the early phases of CKD diagnosis for screening patients at risk of rapid CKD progression and severe complications. Accordingly, therapy should begin in the early stages. Dr. Nikolova emphasizes the importance of initiating a low-phosphate diet early, significantly reducing the risk of severe bone changes associated with secondary hyperparathyroidism, as well as left ventricular hypertrophy and heart failure—complications triggered by FGF-23's effects on the myocardium. She argues that PTH testing alone is insufficient to understand the nature and degree of bone-mineral disorders in CKD patients. Especially in the early stages, PTH changes are less pronounced than those of FGF-23. The conclusion is that FGF-23 is "the missing puzzle piece" in the pathogenesis of mineral-bone disorders and elevated cardiovascular risk in CKD patients.

A conducted study did not find a statistically significant relationship between calcium levels (p=0.171 for FGF-23 and p=0.053 for PTH). These findings, also established by other authors, clearly show the inadequacy of past calcium replacement therapy in CKD patients, as this treatment leads to long-term calcium deposits in vessels and heart valves without reducing fracture risk.

The discussion, spanning 18 pages, is thorough, addressing the obtained results, correlations between studied indicators, hypotheses, proofs, and available literature data.

The bibliography includes 129 references, of which 8 are Bulgarian authors. Twenty-five of the sources are from the last five years.

3   Conclusions of applied significance:

1. Dr. Nikolova achieves the stated aim by gathering extensive evidence and analysis to help define the place of the FGF-23 biomarker in routine clinical practice. The dissertation proves that measuring FGF-23 levels in CKD diagnosis is important and can identify patients at risk of developing severe hyperparathyroidism and mineral-bone disorders within two years.

2. Patients at risk for faster CKD progression can be identified.

3. Using FGF-23 can improve the dietary management of patients.

4. In dialysis patients, FGF-23 can reflect the effectiveness of dialysis procedures regarding phosphate clearance.

5. Since CKD accelerates all cardiovascular risk factors and is itself a strong independent risk factor, identifying high-risk patients is essential for clinical practice. The risk of these patients experiencing a fatal cardiovascular event is greater than the risk of reaching dialysis or transplantation. Searching for predictors of such risk and giving therapeutic guidance is an ongoing process. This dissertation investigates this issue and makes important conclusions in this regard. Using FGF-23 together with other predictors can contribute to a more comprehensive risk assessment.

6. This marker can be used to predict prolonged hypophosphatemia and muscle weakness in patients after kidney transplantation.

4 Contributions of theoretical and confirmatory character:

1. For the first time in Bulgaria, a study of FGF-23 among CKD patients in pre-dialysis and dialysis stages has been conducted.

2. Data are presented on changes in FGF-23 and PTH levels in CKD stages 3–5.

3. Patients are considered in the context of the new CKD-MBD concept and its link to cardiovascular diseases.

4. The relationship of FGF-23 with phosphorus, PTH, and eGFR levels is confirmed.

5. The effect of calcitriol treatment on PTH levels (but not on FGF-23 levels) is confirmed.

6. The analysis of the results provides new directions in the diagnosis and therapy of CKD patients.

7. The dissertation logically leads to its corresponding conclusions.

Dr. Nikolova has sufficient publications on the topic, including one in a journal with an impact factor.

5 Final assessment:

In conclusion, I consider that the dissertation titled *"The Role of Fibroblast Growth Factor 23 in the Development of Renal Bone Disease and Cardiovascular Complications in Patients with Chronic Kidney Disease"*, developed by Dr. Dilyana Nikolova under the supervision of Assoc. Prof. Aleksandar Osichenko, meets all the requirements for awarding the educational and scientific degree "Doctor." Therefore, I express a positive opinion and recommend that the esteemed members of the scientific jury vote **"in favor."**

Sofia, 11.09.2025

Respectfully: Prof. Kundurdzhiev, DM , Ph.D