OPINION

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On the dissertation entitled *"The Role of Fibroblast Growth Factor 23 in the Development of Renal Bone Disease and Cardiovascular Complications in Patients with Chronic Kidney Disease"*
by Dr. Dilyana Mihaylova Nikolova, independent doctoral student under the supervision of Assoc. Prof. Alexander Osichenko, M.D., Ph.D.,
for awarding the educational and scientific degree "Doctor" in the doctoral program within Higher Education Area 7: Healthcare and Sports,
Professional Field 7.1: Medicine.

The dissertation submitted for my review contains 106 pages and is illustrated with 38 figures and 9 tables. The cited literature includes 129 sources, 8 in Cyrillic and 121 in Latin script.

Its structure follows the standard format for a dissertation: introduction, literature review, aims and objectives, materials and methods, results, discussion, conclusions, scientific contributions, references, publications, and scientific communications. I consider the proportions of the individual sections appropriate and corresponding to their respective purposes.

Chronic kidney disease (CKD) carries high social and medical risk, linked to rapid progression and the need for transplantation both nationally and globally. CKD is associated with increased cardiovascular risk. Comorbidities are commonly related to the high incidence of diabetes mellitus and arterial hypertension. Disorders of calcium-phosphate metabolism (serum calcium, phosphate, alkaline phosphatase, parathyroid hormone) are critical for the onset of CKD.

This dissertation addresses one of the most significant problems in clinical nephrology and internal medicine. The investigation of FGF-23, which is the subject of this work, is related to studying disturbances in calcium-phosphate metabolism and their connection to cardiovascular and endocrine diseases. The literature review—comprehensive, well-informed, and timely—is one of the strengths of the dissertation.

The dissertation provides in-depth data and analyzes various patient groups, evaluated using surveys, measurement tools, and laboratory methods. FGF-23 was measured by the Simple Plex™ assay (Ella ProteinSample, USA), alongside eGFR, calcium, parathyroid hormone, inorganic phosphate, and alkaline phosphatase. The statistical analysis is modern and meets the requirements for a dissertation.

The aim is clearly and precisely formulated, logically following from the literature review: to determine the place and role of FGF-23 testing in the diagnostic and therapeutic process for CKD patients, and its association with major cardiovascular events, arterial hypertension, and heart failure.

The six research tasks relate to changes in calcium-phosphate metabolism indicators and their connection to renal, cardiovascular, and endocrine diseases.

A prospective study followed 103 patients treated in the Nephrology Department of the Internal Medicine Clinic at Acibadem City Clinic Tokuda Hospital between 2022 and 2024, equally divided by sex, with a mean age of 70.47 years. A full range of instrumental, clinical,

biochemical, and other laboratory methods was applied to assess their pathology. The statistical processing is well executed and meets evidence-based criteria.

The obtained results are clearly illustrated with tables and figures. To achieve the research aim, Dr. Nikolova set six tasks; their completion ensured reliable results that fulfilled the stated objective.

The dissertation presents a complete and detailed analysis of renal function disturbances and evaluates changes in PTH and FGF-23 levels. These are linked to the use of early markers of bone density changes to maintain calcium-phosphate homeostasis.

By emphasizing the early initiation of a low-phosphate diet, the author proves a significant reduction in the risk of severe bone changes associated with secondary hyperparathyroidism, as well as left ventricular hypertrophy and heart failure—complications caused by FGF-23 effects on the myocardium. As renal insufficiency progresses, these changes escalate and become increasingly difficult to treat.

The data from Dr. Nikolova's study identify FGF-23 as an important laboratory marker in the early phases of CKD diagnosis, useful for screening patients at risk of rapid disease progression and severe complications. These findings indicate that therapy for bone-mineral disorders should begin in the early phases of the disease, long before deviations in serum calcium and phosphate levels become evident.

The discussion is competently executed, thoroughly and objectively analyzing the results and comparing them with literature data. Based on the findings and conducted research, six conclusions were drawn. There are six contributions, each with original and confirmatory scientific-applied potential.

The bibliography includes a large number of contemporary scientific sources dedicated to the issues studied in the dissertation. Notably, 129 sources are cited, most of which are recent (from the last five years). Of these, 121 are in Latin script and 8 in Cyrillic, covering original works on CKD, hyperparathyroidism, and calcium-phosphate metabolism disturbances.

A list of seven publications is presented, including participation in national and international congresses, posters, and articles related to the dissertation topic, with the doctoral candidate as the first author in six of them.

The abstract fully reflects the content of the dissertation.

Dr. Dilyana Nikolova is a nephrology specialist with over 13 years of experience in the field and seven years as an assistant at Aleksandrovska Hospital in the Clinic of Nephrology and Transplantology. She earned her Internal Medicine specialization in 2005 and speaks English and German.

Conclusion:
This dissertation addresses a clinical problem of great health, socio-economic, and scientific significance. Dr. Nikolova competently examines essential aspects of the pathogenesis of calcium-phosphate metabolism. For the first time in Bulgaria, FGF-23 research among CKD patients in pre-dialysis and dialysis stages has been conducted. The results are of theoretical, scientific, and practical significance.

I believe that the dissertation *"The Role of FGF-23 in the Development of Renal Bone Disease and Cardiovascular Complications in Patients with Chronic Kidney Disease"* meets the requirements for awarding the educational and scientific degree "Doctor" in Internal Medicine to Dr. Dilyana Mihaylova Nikolova. I confidently suggest that the esteemed jury vote positively.

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