Editorial

Lorenza Magagnoli, Andrea Galassi, Paola Ciceri and Mario Cozzolino*

Measuring FGF23 in clinical practice: dream or reality?

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In recent years, nephrologists have dreamed of a time when they could measure fibroblast growth factor 23 (FGF23) levels in their patients with chronic kidney disease (CKD). Indeed, in addition to the usual enthusiasm that accompanies many new discoveries, the initial results on FGF23 were so impressive that they quickly led to the idea that this biomarker could play a relevant role in clinical practice.

Belonging to the subfamily of endocrine fibroblast growth factors, FGF23 is physiologically secreted from the bone to induce negative phosphate balance. In fact, it acts on the kidney, promoting phosphate excretion and inhibiting vitamin D activation, on the parathyroid glands, suppressing the secretion of parathyroid hormone (PTH), and on the digestive tract, reducing phosphate absorption. In CKD, FGF23 levels increase as a compensatory mechanism to maintain phosphate homeostasis. As disease progresses, this compensatory mechanism becomes maladaptive and leads to an impending progressive derangement in mineral homeostasis, and to the development of CKD Mineral and Bone Disorder (CKD-MBD) [1, 2]. In addition to phosphate balance, FGF23 may be directly involved in iron metabolism and erythropoiesis, inflammation, insulin resistance, proteinuria, acute kidney injury and left ventricular hypertrophy [3, 4].

In following patients with CKD, nephrologists usually monitor the trajectories of calcium, phosphate, vitamin D and PTH, trying to keep them balanced and reduce the risk of bone and cardiovascular (CV) diseases [5]. However, there are several reasons why they would like to be able to monitor FGF23 as well. First, increased FGF23 levels may be one of the earliest detectable biomarkers of CKD-MBD, preceding the development of hyperparathyroidism and hyperphosphatemia [6]. Moreover, many observational studies have suggested that elevated FGF23 in patients with CKD is strongly associated with worsening renal function, higher risk of death and increased incidence of cardiovascular disease [7–9]. In sight of these data, monitoring FGF23 in CKD patients could help nephrologists to identify those who need closer follow-up, or stronger prevention measures. Moreover, we could imagine that directly targeting FGF23 levels could improve survival and reduce morbidity in CKD patients, although a prospective and properly designed trial is needed to test this hypothesis.

However, we are aware that promising findings on clinical outcomes are not sufficient to make the clinical use of a new biomarker meaningful. In fact, other factors must be taken into account, such as analytical validity, clinical validity and clinical utility [10, 11], summarized in Table 1. Considering all these elements, is it still possible to hope that FGF23 will soon be used in our nephrology centers?

In this issue of the Journal, an interesting review by Ferraro et al. helps us taking stock of the situation. Through the evaluation of 52 original papers published from 1965 to May 2022, the authors present what it is known on analytical validity and clinical utility of FGF23 determination in CKD [12]. In the first part, they examine several analytical issues concerning this biomarker. Although clinicians might be disheartened by such a technical topic, this knowledge is necessary for a critical reading of previous epidemiological studies on FGF23. In fact, some analytical factors may be responsible for their disagreeing results, such as a great heterogeneity among assay design and epitope recognition, the lack of a reference material and harmonized assays, and some pre-analytical stability issues. Then, the authors focus on the role of FGF23 as a CV marker in CKD. They address that FGF23 concentrations display a wide diversity between different CKD stages and also within the same stage (e.g. dialysis patients), in contrast to other established CV biomarkers, of which high levels are associated with adverse outcomes across all

*Corresponding author: Correspondig author: Mario Cozzolino, MD, PhD, FERA, FASN, Renal Division and Laboratory of Experimental Nephrology, Dipartimento di Scienze della Salute, ASST Santi Paolo e Carlo, Università di Milano, Renal Division, S. Paolo Hospital, Milan, Via A. di Rudinì, 8 – 20142, Milan, Italy, Phone: 02/81844215, Fax: 02/81844473, E-mail: mario.cozzolino@unimi.it
Lorenza Magagnoli and Andrea Galassi, Renal Division, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy
Paola Ciceri, Department of Health Sciences, Laboratory of Experimental Nephrology, University of Milan, Milan, Italy

Table 1: Clinical use of biomarkers.

Parameter	Definition	Components
Analytical validity	Ability to accurately and reliably measure the analyte of interest in the clinical laboratory, and in specimens representative of the population of interest	Analytic sensitivity Analytic specifity Repeatability of test results Assay robustness
Clinical validity	Ability to accurately and reliably predict the clinically defined disorder of interest	Clinical sensitivity Clinical specificity Predictive values
Clinical utility	Ability to improve measurable clinical outcomes and improve the current clinical practice	Efficacy Effectiveness Balance of benefits and harms
Contextual issues	Other clinical, economic, psychological and ethical considerations	Severity of the disorder Therapeutic alternatives Diagnostic alternatives Availability and use of the test Cost Cost-effectiveness Opportunity costs Insurability Family factors Acceptability Equity/fairness

Adapted from making meaningful clinical use of biomarkers [10].

CKD stages. Therefore, they suggest that future research should focus on providing different FGF23 threshold for risk classification based on kidney function. Some factors that may explain the high intra- and inter-variability of FGF23 in hemodialysis patients are discussed in the third section of the manuscript. Here, the authors underlie the importance of establishing the best time for sample collection, as overhydration and dialysis session may influence the results. Moreover, researchers should account for differences in half-life and the biological variability between iFGF23 and cFGF23, especially when used as a measure of treatment effect. Finally, data on FGF23 in children with CKD are presented and the authors speculate that its value as a CV risk factor could be even greater in children and adolescence than in adults, due to the lack of pre-existing CV disease and of other traditional risk factors.

Although reading this review most nephrologists may feel disappointed and discouraged by all the described issues, they will eventually find a message of hope in the concluding remarks. Obstacles met along the way should not intimidate researchers, but rather encourage them. In fact, as the authors suggested, all the aforementioned issues must be acknowledged to design appropriate future trials, and clinical researchers should pay more attention in pre-analytical sampling conditions, analytical methods, and statistical analysis including adequate sample size estimation given the wide dispersion of FGF23.

Certainly, more robust evidence is needed for clinical validation of FGF23 in CKD, and there are many questions that have yet to be answered with future research. However, we agree with Ferraro et al. on two important points. First, the evolution of analytical techniques for FGF23 determination has contributed to reveal its pathophysiological role and may lead to novel therapeutic approaches. Second, few biomarkers have shown such a strong linkage with hard clinical end points. Therefore, even if it is not yet the time for nephrologists to have FGF23 among the tests available for their CKD patients, we can still believe that this moment will come in the near future.

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