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Do FGF23 levels change over time and if yes, what do such changes mean?

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FGF23, mortality risk, cardiovascular disease, chronic kidney disease

FGF23 has emerged as a novel and exciting risk factor of adverse outcomes in patients with CKD, ESRD and kidney transplant [1–3]. FGF23 is a hormone produced in the bones. Its main physiologic roles are the enhancement of phosphaturia and the suppression of $1,25(OH)_2$ vitamin D levels [4]. To date, there is debate about the mechanisms whereby FGF23 may

induce adverse outcomes, and specifically cardiovascular complications [5]. One possibility is that FGF23 is merely another marker of disordered bone-mineral metabolism, abnormalities of which are well-established risk factors for adverse outcomes in patients with kidney disease [6]. However, the magnitude of the risk imparted by elevated FGF23 levels is disproportionately high compared with other components of bone-mineral metabolism [1], which raises the possibility that high FGF23 may exert its negative impact through distinct mechanisms of action independent from its role as a regulator of phosphorus homeostasis. First, FGF23 may be involved in numerous physiologic processes beyond the regulation of phosphorus homeostasis, which could themselves be implicated in the causation of various adverse outcomes given an unchecked elevation of FGF23 [7, 8]. Second, elevated FGF23 levels have been associated with increased mortality in populations with normal kidney function [9], suggesting that the presence of CKD and its myriads of various complications is not a prerequisite for the negative effects associated with FGF23. Some of the mechanisms unrelated to classic FGF23 physiology that have been suggested as instrumental in its adverse effects are the engenderment of left ventricular hypertrophy [10], the activation of the renin–angiotensin–aldosterone system [7] with its multiple deleterious downstream effects, the enhancement of inflammation [7, 11], or downstream effects related to its lowering of circulating α-klotho levels [7, 12].

The current level of evidence (consisting of multiple observational studies and compelling animal and *in vitro* experimental data) suggests that FGF23 may indeed be a causative factor in the excess cardiovascular morbidity and mortality seen in CKD and ESRD [13]. However, in order to prove this hypothesis we need to be able to show that therapeutic lowering of FGF23 in humans can alleviate the various cardiovascular consequences attributed to its elevated levels in observational and in animal studies. To date there have been no such human studies. Animal experiments using antibodies to completely block FGF23 have had controversial results: successful obliteration of FGF23 effects achieved correction of both secondary hyperparathyroidism and low vitamin D level, and also the normalization of bone structure and turnover rate, but it also resulted in the development of hyperphosphatemia, in a significant increase in aortic calcification and in increased mortality [14]. These experiments suggest that FGF23 may have vital physiologic roles and its complete absence could be just as deleterious as extreme elevations in its levels. Studies like these should make us pause before we embark on long and costly human clinical trials, and should prompt us to gather more compelling evidence towards the putative benefits of therapeutic FGF23 lowering. A potential interim solution is the examination of the effects of FGF23 change over time in observational studies, which, if well designed, could mimic the effects of randomized controlled trials of FGF23 lowering [15].

Most of the observational literature has examined the association of static FGF23 levels with future outcomes, which offers no answer to what might happen if a patient were to experience an intervention to decrease its levels. An excellent paper in this issue of the journal tries to examine this latter question [16]. The authors of this study sought to describe how FGF23 levels changed over time, and whether these changes had any effect on subsequent clinical outcomes in patients with CKD. This was a *post hoc* analysis of data from the MASTERPLAN study, a clinical trial performed in patients with CKD in nine Dutch hospitals. In the 439 patients eligible for participation, FGF23 was measured at baseline and after 2 years, and was found to be remarkably stable: only 21.6% of all patients showed a change in their baseline FGF23 levels (in 10.7% it increased, and 10.9% it decreased over time). Overall there has been a modest increase in median FGF23 levels, perhaps due to the fact that the kidney function of the participants declined slightly during the follow-up. Elevated FGF23 levels were associated with the primary outcome of the composite of myocardial infarction, stroke and cardiovascular mortality and with the secondary end points of overall mortality, congestive heart failure and start of renal replacement therapy. The outcomes were almost identical if considering baseline FGF23 and time-averaged FGF23. Interestingly, change in FGF23 did not show an association with the studied outcomes except for an association with a higher rate of renal replacement therapy initiation. The latter observation is perhaps not surprising, considering that increases in FGF23 are closely correlated with decreases in GFR, and consequently also with a host of other abnormalities (e.g. volume overload, electrolyte, acid–base and bone-mineral abnormalities) that may all serve as potential indications for dialysis initiation, but many of which were not accounted for in this study.

The study by Bouma-de Krijger *et al.* offers important and novel lessons. It is one of the first studies that examined FGF23 repeatedly and the first to correlate change in FGF23 with outcomes in a substantial number of individuals with CKD, showing that its levels are remarkably stable over time, and that associations derived from repeat measurements did not add substantially to those obtained from single measurements. A previous study by Scialla *et al.* also examined temporal changes in FGF23 in African-American patients with CKD [17]. This study found that changes in FGF23 were tightly correlated with changes in measured GFR; the reasons why there seemed to be more substantial change in FGF23 levels in this versus the study by Bouma-de Krijger may have been due to the less pronounced temporal change in kidney function seen in the latter one. Based on these two studies, it thus appears that future studies may be able to use single measurements of FGF23 both for risk-stratification purposes, and for establishing baseline levels for interventional trials, as long as temporal changes in kidney function are properly accounted for. Considering how pricey the measurement of FGF23 remains, this finding is very important from a practical perspective.

The second question that the study by Bouma-de Krijger sought to answer is the one pertinent to clinical interventions, namely if a decline in FGF23 over time would be associated with a decrease in the subsequent risk of the studied outcomes. While the results from this study did not show a significant association of a temporal decline in FGF23 with clinical outcomes, it is important to emphasize that only a small proportion of patients experienced a decrease in FGF23 levels, and the number of events was so small in this select group, that it is does not allow us to

reliably answer this question. Furthermore, the reason for the decrease in FGF23 levels over time are unknown, and hence it is not possible to determine if such decrease happened due to some kind of therapeutic intervention (e.g. the application if a non-calcium type phosphate binder over an extended period of time [18–20]), or to a fundamental change in the physiologic milieu governing FGF23 production. Knowledge of these factors would be essential if we were to determine a cause–effect relationship between a decrease in FGF23 and outcomes, because any or all of these factors could act as confounders (i.e. they could independently affect not only FGF23 levels but also the studied outcomes [21]), and the lack of adjustment for their effects would give the erroneous impression that FGF23 change has an independent effect on outcomes. These remaining questions will have to be answered in future studies, with large enough sample sizes, with more substantial changes in FGF23 levels and with sufficiently high event rates that would allow properly complex analyses to mimic therapeutic interventions in clinical trials.

In summary, FGF23 is again confirmed as an important predictor of major clinical events in patients with CKD. Single measurements in FGF23 seem to reliably represent an individual's FGF23 status over time as long as their kidney function remains relatively stable, suggesting that it could be used both as a risk factor and as a baseline measure for therapeutic interventions in the future. At this time, it remains unclear what the effects of therapeutic lowering of FGF23 might be. Prior to embarking on long, costly and potentially hazardous clinical trials of therapeutic FGF23 lowering, it may be advantageous to examine the potential effect of declining FGF23 levels in larger observational studies, which would have sufficient power to reliably detect the true effects associated with temporal changes in FGF23, and that contain detailed enough information to allow for complex statistical analyses that address the numerous biases inherent of observational studies.

CONFLICT OF INTEREST STATEMENT

The author has received consultancy fees from Amgen and grant support from Shire.

(See related article by Bouma-de Krijger *et al.* Time-averaged level of fibroblast growth factor-23 and clinical events in chronic kidney disease. *Nephrol Dial Transplant* 2014; 29: 88–97.)

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