FGF23 antagonism: the thin line between adaptation and maladaptation in chronic kidney disease

Markus Ketteler,
Patrick H. Biggar and Orfeas Liangos

Division of Nephrology, Klinikum Coburg GmbH, Coburg, Germany

Correspondence and offprint requests to: Markus Ketteler; E-mail: markus.ketteler@klinikum-coburg.de

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ABSTRACT

For more than 10 years, we have been convinced by overwhelming epidemiological evidence with a high biological plausibility that hyperphosphataemia imposes one of the most sustained cardiovascular and mortality risks on patients suffering from chronic kidney disease (CKD). With the discovery of the fibroblast growth factor-23 (FGF23)/klotho axis, we not only gained a new and mechanistic understanding of phosphate handling of the body, we also felt that novel therapeutic strategies may arise counteracting the deleterious consequences of phosphate retention, dysregulation and maldistribution. Two recent experimental studies shed additional and important light on what we can expect from such new insights. Faul et al. showed us that FGF23 excess may directly induce left ventricular hypertrophy (LVH) and that FGF-receptor antagonism ameliorates CKD-induced LVH in rats. Shalhoub et al. have now added preclinical data to this scenario by indeed supporting the notion that FGF23 antagonism effectively blocks the development of most of the characteristics of secondary hyperparathyroidism in a rat model of CKD, albeit at the cost of hyperphosphataemia, vascular calcification and premature death. This important scientific work indicates that the observed laboratory derangements in chronic diseases may—at least to some degree—merely reflect the body’s best possible means to adapt to otherwise inevitable functional derangements. With regard to CKD, these new data furthermore suggest that protection from hyperphosphataemia may be the ultimate goal to achieve substantial longevity in CKD.

INTRODUCTION

The discovery of the fibroblast growth factor-23 (FGF23)/klotho axis has most significantly impacted on our understanding of the biology and pathophysiology of chronic kidney disease—bone and mineral disorders (CKD-MBD) in the recent years [1–3]. FGF23 developed from the master regulator of phosphate handling to one of the most potent mortality risk predictors in CKD and, most recently, to an intriguing pathogenic factor mediating cardiovascular damage [4]. Therapeutic concepts have already been designed targeting earliest elevations of FGF23 in the time course of CKD, e.g. by restricting phosphate exposure [1]. Furthermore, FGF23 antagonism is considered as one of the most promising treatment approaches towards preventing the cardiac sequelae associated with CKD, as evidenced in the recent seminal translational paper by Faul et al. [4] demonstrating direct induction of left ventricular hypertrophy (LVH) by FGF23 in rodents. Shalhoub et al. [5] have now added preclinical data to this scenario by indeed supporting the notion that FGF23 antagonism effectively blocks the development of most of the characteristics of secondary hyperparathyroidism in a rat model of CKD, albeit at the cost of hyperphosphataemia, vascular calcification and premature death. This important scientific work indicates that the observed laboratory derangements in chronic diseases may—at least to some degree—merely reflect the body’s best possible means to adapt to otherwise inevitable functional derangements. With regard to CKD, these new data furthermore suggest that protection from hyperphosphataemia may be the ultimate goal to achieve substantial longevity in CKD.

FGF23—THE MASTER REGULATOR OF PHOSPHATE HOMEOSTASIS

It is now nearly a decade ago that work in FGF23-deficient mice identified this hormone’s pivotal role in mineral homeostasis in mammals [6]. FGF23 is a bone-derived hormone secreted from osteocytes. Loss of FGF23 function resulted in severe hyperphosphataemia (increased tubular phosphate reabsorption) and endogenous calcitriol intoxication (induction of renal 1-α-hydroxylase), with subsequent hypercalcaemia and parathyroid hormone (PTH) suppression. The lifespan of these
animals was greatly reduced. Of note, the same phenotype had been observed in mice deficient of klotho, a transmembrane β-glucuronidase, which in this context was identified as the essential second part of a dimeric FGF23 receptor at kidney and parathyroid tissues [7]. Activation of this receptor inhibits two tubular sodium-phosphate transporters (NaPi-IIa and -IIc) greatly limiting the capacity of phosphate reabsorption from the urine [3]. PTH, as the other potent phosphaturic hormone, principally acts on the same transporters, however, through different receptor and signal transduction pathways. In a greater context, this means that the organism employs two complex and potent hormonal systems in order to protect itself against hyperphosphataemia as robust as possible.

FGF23 directly inhibits PTH secretion, but this effect is clinically overridden in CKD by progressive calcitriol deficiency and by the stepwise development of parathyroid klotho resistance in progressive uraemia. Furthermore, FGF23 and calcitriol form a feedback cycle with FGF23 suppressing 1,25-(OH)2-vitamin D hydroxylation, and calcitriol inducing FGF23 expression and secretion from the bone [2, 8].

In the clinical setting, it was subsequently reported that FGF23 serum levels already start to rise in early CKD stages, while normophosphataemia is mostly maintained well into CKD stages 4–5 [9, 10]. Recent work by Isakova et al. [11] indicated that increases in FGF23 may be the very first detectable laboratory aberration in the development of CKD-MBD, well before rises in serum PTH or phosphate concentrations. In CKD stage 2, approximately 40% of individuals were already shown to have elevated FGF23 levels in this large observational study.

In CKD-5D patients, FGF23 serum concentrations may rise enormously: while healthy individuals display FGF23 blood levels of 30–70 RU/mL (mostly measured by the C-terminal assay), these levels may rise up to 100 000 RU/mL in dialysis patients [1]. The available studies in dialysis cohorts mostly demonstrate a robust correlation with serum phosphate concentrations [12–14].

Based on the physiology of the FGF23/klotho system, preliminary clinical attempts were made to suppress FGF23 upregulation by phosphate binder treatment. However, most of these studies were short-term and observed only quite small cohorts, and results so far have remained inhomogenous, ranging from no effect to FGF23 suppression [15]. Calcimimetics may decrease FGF23 secretion, while it seems unclear, whether this is a direct effect or mediated via lowering serum phosphate levels [16]. As expected, calcitriol and paricalcitol have been shown to be reproducibly increase FGF23 serum levels [17].

FGF23—MORTALITY RISK FACTOR IN CKD AND BEYOND

Gutiérrez et al. [14] published the first study demonstrating that FGF23 was a strong and independent risk predictor of mortality in incident dialysis patients. This risk prediction was especially remarkable in patients with no or only moderate hyperphosphataemia. This first report was subsequently followed by observational studies in prevalent dialysis patients and in predialysis stages of CKD, all indicating FGF23 as one of the most powerful mortality risk factors [13, 18, 19]. Additional studies related high FGF23 serum levels to faster progression of CKD, to an increased likelihood of renal transplant failure and to subclinical CKD in the elderly [20–22].

Parker et al. [23] recently studied FGF23 in the Heart and Soul study cohort consisting of cardiovascular risk patients, of which the majority had normal or only modestly reduced renal function. Even in this group, FGF23 predicted a significantly impaired survival in those subjects in the highest tertile of FGF23 levels (>56.7 RU/mL, which approximates the upper normal range of the assay for healthy adults). These results were recently supported by data from a large non-CKD cohort (Cardiovascular Health Study) associating FGF23 levels with all-cause mortality and incident heart failure [24]. Another study in community-dwelling adults with preserved renal function (Health Professionals Follow-up Study) focused on factors predicting higher FGF23 serum levels and especially reporting associations with cardiovascular comorbidities (age, BMI, hypertension, smoking etc.) and some elevated laboratory parameters (elevated phosphate, PTH etc.) [25]. Consequently, the questions arise, whether FGF23 may be a kidney function-dependent surrogate of another risk imposing scenario, and which absolute magnitude of FGF23 concentrations may represent a danger signal in which population.

FGF23 AND THE CARDIOVASCULAR SYSTEM: NON-RENAL EFFECTS WITH GREAT IMPACT

With regard to cardiovascular morbidity in CKD, the key question was whether FGF23 may be the more lucid reflection of phosphate-induced cardiovascular damage, or whether FGF23 actually targets and damages cardiovascular structures? One could imagine that enormously elevated FGF23 concentrations in dialysis stages may, for example, induce pathological effects by activation of unspecific FGF receptors. Myles Wolf’s group has not only taken the lead in this field, but continues to precisely shape the understanding of FGF23 biology in CKD and beyond. Indeed, they first showed that FGF23 correlated to the presence of LVH in CKD patients [26]. Their observation, as well as the above-mentioned risk associations in non-CKD cohorts, was recently confirmed and strongly emphasized by Seiler et al. [27] showing the same LVH association in a cardiovascular cohort with no or only slightly impaired renal function. Furthermore, this group demonstrated a unique and strong relationship between FGF23 and atrial fibrillation in this group of patients, rather than linking FGF23 to classical atherosclerotic cardiovascular disease [27].

Faul et al. [4] published an outstanding collaborative and translational paper outlining first the strong clinical association between FGF23 and left ventricular mass index, impaired ejection fraction and concentric and eccentric remodelling in CKD patients. Then, the group documented that FGF23 injections caused LVH in rodent models. In
parallel, it was shown that this FGF23-induced myocardial remodelling was not klotho-dependent and that calcineurin-nuclear factor of activated T cells was involved in myocardial FGF-receptor signal transduction. Finally, when inducing CKD in rats by 5/6-nephrectomy (5/6-Nx), causing hypertension and LVH, LVH could be significantly and blood pressure independently reduced by the administration of a non-specific FGF-receptor blocker [4]. Based on these data, FGF23 evolved from a biomarker of disease severity to one of the most suggestive mediators of CKD-associated cardiovascular morbidity. Now, the stage was set to strongly consider further exploring the idea of FGF23 antagonism in order to reduce morbidity in models and cohorts at risk, especially in the setting of CKD.

**FGF23 AS A TREATMENT TARGET**

This is how the recent paper by Shalhoub et al. [5] now fits in. These investigators first established a neutralizing FGF23-specific antibody and then employed it, as Faul et al. did, in the well-established rat CKD model of 5/6-Nx. This model develops all characteristic features of CKD-MBD, including secondary hyperparathyroidism, calcitriol deficiency, hyper-phosphataemia and secondary FGF23 excess. To enhance CKD-MBD, a high-phosphate diet (HPD) was fed. Thus, five groups of animals were observed: (i) normal rats on normal phosphate diet, receiving control antibody; (ii) sham-operated rats on HPD, receiving control antibody; (iii) 5/6-Nx on HPD, receiving control antibody; (iv) 5/6-Nx on HPD, receiving low-dose FGF23 antibody (3 mg/kg body weight [b. w.]) and (v) 5/6-Nx on HPD, receiving high-dose FGF23 antibody (10 mg/kg b.w.). The rationale of this study was to test the potential adaptive versus the maladaptive properties of FGF23 in this model of progressive CKD.

Most biochemical results appeared straightforward and predictable based on the current knowledge of FGF23 physiology. FGF23 antagonism led to a dose-dependent increase in serum phosphate levels associated with a variable reduction in fractional phosphate excretion (but without overall reductions in 24-h urinary phosphate excretion). Calcitriol levels were higher especially in the high-dose FGF23 antibody-treated group with increasing serum calcium levels, and serum PTH levels consequently decreased with FGF23 antagonism. In parallel, improvements of high-turnover renal osteodystrophy were observed to be associated with FGF23-antibody treatment. Some expected features (e.g. changes in tubular NaPi-IIa and Cyp24a1 expression) may not have been observed because of counter-regulatory actions of treatment-induced shifts in calcitriol and PTH.

Unlike the findings by Faul et al., this experimental approach did not show amelioration of LVH by FGF23 antagonism. However, there were a few strategic differences in targeting FGF23 excess between these two studies. Shalhoub et al. [5] administered an FGF23-specific antibody only when CKD was firmly established, while the former study used a non-specific FGF-receptor blocker starting immediately after the 5/6-Nx surgical procedure, thus, in a more preventive fashion. The other difference was the exposure of rats to a HPD versus a normal phosphate diet [4]. Table 1 depicts similarities and differences between these two investigations.

**Table 1. FGF23 antagonism in the rat model of 5/6-Nx [4, 5]**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>No effect on LVH</td>
<td>LVH ↓</td>
<td>Non-specific FGF-receptor blocker</td>
</tr>
<tr>
<td>Effect on BP n.d.</td>
<td>No effect on BP</td>
<td></td>
</tr>
<tr>
<td>sHPT ↓</td>
<td>CKD-MBD parameter n.d.</td>
<td></td>
</tr>
<tr>
<td>Vascular calcification ↑</td>
<td></td>
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<tr>
<td>1,25-(OH)2-D↑</td>
<td></td>
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</tr>
<tr>
<td>Bone turnover ↓</td>
<td></td>
<td></td>
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<tr>
<td>Hyperphosphataemia</td>
<td></td>
<td></td>
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<tr>
<td>Mortality ↑</td>
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Ab: antibody; LVH: left ventricular hypertrophy; sHPT: secondary hyperparathyroidism; BP: blood pressure; n.d.: not determined; 1,25-(OH)2-D: calcitriol; CKD-MBD: chronic kidney disease-mineral bone disorder.

**IS CKD ALL ABOUT PHOSPHATE?**

The key observation in this most recent study by Shalhoub et al. was that the use of specific FGF23 antibodies in an animal model of CKD led to increased mortality, despite some ‘favourable’ effects on the majority of classical parameters of CKD-MBD and particularly on the development of secondary hyperparathyroidism. Hyperphosphataemia was assumed to be the mediator of mortality leading to accelerated calcification in animals following FGF23 antagonism. However, an important question remains: what would have been the course of the disease, if normal or low dietary phosphate would have been fed after 5/6-Nx instead of a HPD? In any case, directly antagonizing FGF23 means antagonizing the phosphaturic defences of the body (obviously including PTH), which may be the pivotal priority in progressive CKD.
Another question is how potent an indirect FGF23 antagonism would be by targeting phosphate (additive) restriction, phosphate binders or phosphate transport inhibitors? Nagano et al. showed convincing preclinical data on FGF23 and PTH suppression by sevelamer in a rodent model of CKD, but no ‘hard outcomes’ or effects on cardiovascular remodelling were published from that model [28]. Moreover, recent clinical trials in earlier stages of CKD, as already pointed out above, yielded quite inhomogenous results regarding phosphate lowering on FGF23 serum levels and surrogate endpoints such as vascular calcification [15, 29]. Finally, the question may be asked whether FGF-receptor-specific antibodies—leaving the physiological FGF23 actions untouched—could be developed into therapeutic options once the culprit receptor causing FGF23-mediated ‘collateral cardiovascular damage’ is distinctly identified.

CONCLUSIONS

What can we learn from two intelligent and translational experimental studies on the role of FGF23 in CKD and cardiovascular morbidity [4, 5]? First of all, FGF23 may indeed be more than a surrogate of impaired phosphate handling and a pathogenic factor on its own. Secondly, FGF23 is a key adaptive mechanism during the course of CKD causing sustained prevention of a substantial threat, i.e. hyperphosphataemia (comparative to secondary hyperparathyroidism). Thirdly, FGF23 may proportionally be a very adequate biomarker with regard to the effective loss of nephron mass (which serum phosphate is not). Therefore, in the current stage of science in this field, it seems impossible to firmly recommend any future therapeutic strategies declaring FGF23 antagonism as a promising target, at least in predialysis stages of CKD. The concept of adaptation versus maladaptation is very complex in chronic disease in general, and we may have learned a little from clinical experience in the field of renal anaemia [30–32]. Just treating because laboratory parameters fail to remain in a supposedly normal range may potentially do more harm than good. Quoting the wording in the kidney disease–improving global outcomes guidelines on CKD-MBD as published in 2009 ‘Chapter 4.2.1: In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known’ [33]. Up to this point in 2012, this also clearly applies to FGF23.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES


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