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Beyond mineral metabolism, is there an interplay between FGF23 and vitamin D in innate immunity?

Justine Bacchetta[1,2,3,*], **Isidro B Salusky**[4], and **Martin Hewison**[5]

[1]Centre de Référence des Maladies Rénales Rares, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France

[2]Université de Lyon, Lyon, France

[3]Institut de Génomique Fonctionnelle de Lyon (IGFL), Ecole Normale Supérieure, Lyon, France

[4]Department of Pediatrics, David Geffen School of Medicine, University of California at Los Angeles, USA

[5]Orthopaedic Research Hospital, University of California at Los Angeles, USA

Abstract

Fibroblast Growth Factor 23 (FGF23) is an 'endocrine' FGF acting in the kidney as a phosphaturic hormone and a suppressor of active vitamin D, through an inhibition of the 1α hydroxylase and a stimulation of the 24 hydroxylase. Beyond its well-known effects on the bone/kidney/parathyroid axis and its deregulation during chronic kidney disease (CKD), recent evidence has revealed its direct systemic effects on cardiovascular health. In the meantime, studies have highlighted health implications for vitamin D inside and outside CKD that also extend beyond its classical actions on mineral homeostasis and bone metabolism: vitamin D has indeed been shown to exert pluripotent non-classical effects as a modulator of immune function in monocytes, mainly through the stimulation of the antimicrobial cathelicidin. The aim of this review is to provide new insights on the interplay between FGF23 and vitamin D in innate immunity in the context of CKD.

Keywords

children; CKD; FGF23; immunity

Introduction

Fibroblast Growth Factor 23 (FGF23) is a protein synthesized by osteocytes and osteoblasts that has recently been shown to have a key role in the 'bone-parathyroid-kidney' axis and the regulation of phosphate/calcium/vitamin D metabolism [1-3]. It acts mainly as a phosphaturic factor, inhibiting the expression of type IIa sodium-phosphate cotransporters

[*]**Corresponding author: Justine Bacchetta, MD, PhD**, justine.bacchetta@chu-lyon.fr, Centre de Référence des Maladies Rénales Rares, Service de Néphrologie et Rhumatologie Pédiatriques, Hôpital Femme Mère Enfant, 59 Bd Pinel - 69677 Bron, France, Tel: +33 4 72 11 93 38, Fax: +33 4 27 85 67 68.

Disclosure of interests
None.

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on the apical membrane of proximal tubular cells, thus leading to inhibition of phosphate reabsorption [4]. FGF23 also suppresses renal synthesis of the active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by inhibiting expression of the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) whilst stimulating the catabolic enzyme vitamin D-24-hydroxylase (CYP24A1) [4, 5]. These effects of FGF23 account for its hypophosphatemic action, but FGF23 can also act outside the kidney. Indeed, FGF23 can stimulate expression of CYP27B1 as well as decrease synthesis of parathyroid hormone in the parathyroid gland, highlighting a potential role in the modulation of localized extra-renal synthesis of $1,25(OH)_2D$ [6, 7]. Over the past decade, numerous studies have documented that FGF23 levels are increased in patients with chronic kidney disease (CKD) and that this hormone is related to alterations in mineral metabolism and to the development of secondary hyperparathyroidism [5, 8-10]. The increase in FGF23 levels in patients with CKD may be due, in part, to decreased renal FGF23 clearance but increased synthesis of FGF23 by osteocytes also occurs as early as CKD stage 2, perhaps in an attempt to maintain renal phosphate excretion in the context of declining renal mass [5, 11, 12]. In addition to its contribution to normal physiological regulation of mineral metabolism, FGF23 appears to be an independent predictor of both CKD progression, development of left ventricular hypertrophy, and mortality in adults with pre-dialysis CKD [13]. High FGF23 circulating levels have been shown to be a risk factor for cardiovascular morbidity and mortality in general adult and dialysis populations [14-18], and elevated serum FGF23 concentrations have also been associated with cardiovascular calcifications in dialyzed children [19]. The recent demonstration of a Klotho-independent effect of FGF23 on rat cardiomyocytes in addition to epidemiological association studies linking FGF23 to left ventricular hypertrophy strongly suggests a causal and toxic role for FGF23 in cardiovascular outcomes [20].

In parallel with these FGF23 data, recent studies have also highlighted health implications for vitamin D and CKD that extend beyond its classical actions on mineral homeostasis and bone metabolism [21]. In particular, vitamin D has been shown to exert pluripotent non-classical effects as a modulator of immune function [22, 23] and, as a result, vitamin D may act as a protective factor against infections, autoimmune disease, cardiovascular disease and cancer [24]. Cells from the immune system such as monocytes express both CYP27B1 and the nuclear vitamin D receptor (VDR) and use intracrine conversion of 25OHD to $1,25(OH)_2D$ to promote innate antibacterial responses to infection [25, 26], mainly through the induction of the antibacterial cathelicidin (CAMP or LL37) [26]. The importance of localized CYP27B1 metabolism in driving innate and adaptive immune activity of vitamin D means that the efficacy of these responses is strongly influenced by availability of the CYP27B1 substrate, 25OHD. As serum levels of 25OHD are a direct marker of patient vitamin D status, it has been proposed that immune function *in vivo* will be compromised under conditions of vitamin D-insufficiency or –deficiency. Low vitamin D status has become more and more prevalent worldwide, due to several combined factors such as decreased sunlight exposure, relative scarcity of vitamin D in occidental diets, lack of supplementation in vitamin D due to the current underestimation for recommended daily intake and increased body fat mass in populations. Current data demonstrated that optimal levels should be above 30 ng/mL (i.e., 75 nmol/L) [22].

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Vitamin D deficiency, defined by a 25OH vitamin D level below 20 ng/mL (or 50 nmol/L) and vitamin D insufficiency, defined by 25OH vitamin D levels between 20 and 30 ng/mL, are highly prevalent in adult and pediatric patients across the spectrum of CKD, as a consequence of several factors such as low dietary intake, chronic illness, skin changes, and sometimes urinary losses in proteinuric patients. At least three pediatric studies focusing on this issue have found similar results: 77% of children presented with vitamin D-deficiency in a cohort of 57 CKD stage 2-4 American children, 26% of children presented with vitamin D deficiency (with a further 32% being vitamin D-insufficient) in a cohort of 143 CKD British children, and 40% of children presented with vitamin D deficiency (with a further 40% being insufficient) in a cohort of 227 CKD stage 1-4 French children [28-30]. Last, in addition to finding a 65% prevalence of vitamin D deficiency in CKD stage 2-4 children, Shroff et al. also recently demonstrated in a placebo-controlled randomized trial that vitamin D_2 (ergocalciferol) was able to delay the onset of secondary hyperparathyroidism in these patients [31].

The aim of this review is to provide new insights on how vitamin D-deficiency in CKD may impact on patient immune function, as well as speculating on the potential added complication of elevated FGF23 levels in this context.

1- Impaired immunity in chronic kidney disease

Apart from the special context of patients with renal transplants [32], CKD by itself is a state of acquired immune deficiency involving both cellular and humoral immunity [33]. The incidence of bacterial infections in dialysis patients is higher than in the general population and acute infections (not only bacterial, but also viral and fungal) substantially contribute to the high hospitalization rates and mortality in patients with end-stage renal disease (ESRD) [34, 35]. For example, in adult hemodialysis patients, mortality rates are increased by 10-fold for pneumonia and 100-fold for sepsis compared to the general population [36, 37]. In the HEMO study which included 1846 adult hemodialysis patients with a mean follow-up of 2.8 years, the annual infection rate reached up to 35% [38]. Data on CKD and infections are relatively scarce in children, but while the survival rate of children with ERSD has improved in the past 20 years, it still remains about 30 times lower than the one expected in a healthy pediatric population, the mortality of these children with ESRD mainly being explained by cardiovascular morbidities and infections [39, 40].

The polymorphonuclear cell dysfunction usually observed in these patients involves increased apoptosis rates and decreased phagocytic properties [41]. However, the increased rates of infection in CKD patients may also be due to other aspects of immune dysfunction including aberrant monocyte, T cell and dendritic cells activity, iron overload, direct effects of uremic toxins, comorbidity conditions such as systemic illnesses, immunosuppressive therapies, anemia, malnutrition or hypoalbuminemia, increased exposure to infectious agents, loss of cutaneous barriers (in case of edema or catheters) and decreased vaccine responsiveness [33, 34, 42].

Vaccines are a potential strategy to reduce morbidity related to infections in CKD and ESRD. However, these patients have a reduced response to vaccinations relative to patients without kidney failure, with both lower rates of vaccine response and a more rapid decline

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of antibody levels after vaccination [34]. In contrast, adequate seroresponse with standard or augmented regimens for vaccinations against influenza, hepatitis B, pneumococcus, and varicella have been documented in patients with CKD [43, 44]; whereas there is emerging evidence of benefit to vaccination in these populations, vaccination rates in adults with CKD/ESRD remain relatively low.

2- From Niels Finsen's Nobel Prize in 1903 to the 2012 concepts on vitamin D effects in innate immunity

An essential function of the innate immune system is to trigger direct antimicrobial mechanisms to defend against invading pathogens. Highly conserved families of pattern recognition receptors are involved in this facet of immunity. Amongst these the toll-like receptors (TLRs) play a critical role in activating host defense pathways, and some of these TLR-mediated responses have been shown to be highly sensitive to vitamin D. In monocytes, activation of TLR2 induces interleukin-15 secretion and bacterial killing, via three key mechanisms: induction of CYP27B1 expression, increased expression of VDR and enhanced transcription of the LL37 gene [45]. Although identical to the one found in the kidney, the CYP27B1 present in extra-renal tissues is regulated in a different fashion to the 'classical' renal CYP27B1 which is predominantly affected by factors associated with calcium/phosphate metabolism [46]. In monocytes and macrophages the regulation and function of CYP27B1 is local, providing high tissue-specific $1,25(OH)_2D$ levels for autocrine and paracrine activity, but without affecting serum concentrations. As such, CYP27B1 expression in monocytes is sensitive to immune stimuli, such as interferon gamma, TLR-ligands such as lipopolysaccharide (TLR4-ligand) or viral infections [46], and is not subjected to $1,25(OH)_2D$ -mediated negative feedback [47]. Localized monocytic expression of CYP27B1 enhances metabolism of 25OHD and the resulting $1,25(OH)_2D$ binds to nuclear VDR, which then induce transcription of the LL37 gene. The resulting antibacterial protein is incorporated into phagosomes where it promotes intracellular killing of infectious pathogens such as Mycobacterium tuberculosis (*M. tb*) [48]. In 2006 Liu *et al.* demonstrated that monocytes incubated in serum with low concentrations of 25OHD were less able to mount an LL37 antibacterial response to *M. tb* than monocytes incubated in serum with normal 25OHD levels [25]. In patients with vitamin D deficiency, Adams et al. have also demonstrated that monocytes increase expression of LL37 after oral supplementation with vitamin D to restore serum 25OHD concentrations to normal [26]. The underlying molecular mechanism behind this regulation of LL37 by vitamin D has been explained by Gombart *et al.*, who showed that vitamin D response elements (VDRE) in the promoter DNA of the human LL37 gene are required to produce the $1,25(OH)_2D$-VDR-mediated regulation of LL37 [49]. This effect was only observed in primates and has been described in several different human cell types [50]. In CKD patients undergoing hemodialysis, serum levels of LL37 in the lowest tertile are an independent risk factor of death attributable to infections [51], highlighting the potential importance of antibacterial responses and vitamin D in the context of infections in CKD.

3- The first off-target effect of FGF23: a Klotho-independent action on cardiomyocytes

In addition to the well-known effects of FGF23 on phosphate and calcium homeostasis, Faul et al recently demonstrated that FGF23 could regulate cardiomyocytes' biology in a Klotho-

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independent manner [20]. Indeed, after a clinical demonstration that the left ventricular mass index was significantly increasing with higher quartiles of circulating FGF23 levels in a prospective cohort of 3070 adults with CKD from the CRIC study and that greater levels of FGF23 levels at baseline were also associated with a higher risk of new-onset left ventricular hypertrophy (LVH) in CKD, the authors studied the effects of FGF23 in cellular (cardiomyocytes from rats) and animal (wild-type mice, Klotho deficient mice and rats with $5/6^{th}$ nephrectomy) models. They showed that FGF23 was able to induce *in vitro* hypertrophy of cardiomyocytes, with an activation of prohypertrophic genes; this effect was dependent of the activation of the FGF-receptors (and notably FGF-R1 and 4). Of note, in contrast to renal or parathyroid cells, these neonatal cardiomyocytes did not express Klotho. Moreover, the main downstream phosphorylation pathway involved in this activation was the PLCγ-calcineurin-NFAT axis (that can be inhibited by the use of cyclosporine), whereas in renal and parathyroid cells exposed to FGF23, the activated pathways are usually rather Erk and Akt [52]. After this cellular demonstration of a direct deleterious effect of FGF23 on cardiac cells, the authors delivered FGF23 in wild-type mice either through a direct myocardial delivery of FGF23 either through an intravenous infusion for 5 days, showing in both conditions the induction of LVH. In a genetic mouse model of high FGF23 circulating levels (i.e., the Klotho deficient mice), they also showed that these mice developed LVH, therefore providing another rationale for a Klotho-independent effect of FGF23 in the cardiovascular system. Last, using a rat model of CKD ($5/6^{th}$ nephrectomy), they showed that a systemic treatment of these animals with the FGFR inhibitor PD173074 was able to attenuate the development of LVH, despite having no effects on the severity of CKD or arterial hypertension.

Thus, all these data provide a mechanistic explanation for the first published off-target effects of FGF23, namely the deleterious effects of FGF23 on cardiomyocytes. These results demonstrate that FGF23 effects can be Klotho-independent, and provide a strong rationale for future clinical trials of FGF23 monoclonal antibodies.

4- FGF23 as a new regulator of innate immunity

Although monocyte vitamin D metabolism and function is known to be stimulated by local factors such as TLR ligands [25, 26], and cytokines [25, 53, 54], it is unclear whether endocrine regulators of CYP27B1 such as FGF23 will exert similar effects. One hypothesis would therefore be that FGF23 could inhibit CYP27B1 in monocytic cells, with concomitant effects on intracrine responses to $1,25(OH)_2D$. We obtained results in both monocytes from healthy donor peripheral blood mononuclear cells (PBMCm) and from peritoneal dialysate effluent (PDm) with *in vitro* FGF23 treatments at 6 and 24 hours [55]. PBMCm and PDm were assessed at baseline to confirm the presence of mRNA for FGF23 receptors (FGFRs), with Klotho and FGFR1 being more strongly expressed than FGFR2/3/4 in both cell types. Immunohistochemistry showed co-expression of Klotho and FGFR1 in PBMCm and PDm; this effect was enhanced following treatment with FGF23 in PBMCm but not PDm. Treatment with FGF23 activated MAP kinase (MAPK) and Akt pathways in PBMCm, demonstrating functional FGFR signaling in these cells. FGF23 treatment of PBMCm and PDm decreased expression of mRNA for CYP27B1. In PBMCm this was associated with downregulation of 25OHD to 1,25(OH)2D metabolism by HPLC analyses, and concomitant

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suppression of intracrine induced 24-hydroxylase (CYP24A1) and antibacterial cathelicidin (LL37). FGF23 suppression of CYP27B1 was particularly pronounced in PBMCm treated with interleukin-15 to stimulate synthesis of 1,25(OH)2D. Thus, it appears that FGF23 could inhibit the extra-renal expression of CYP27B1 and subsequent intracrine synthesis $1,25(OH)_2D$ in these two different human monocyte models [55]. If proved to be true, FGF23 effects in innate immunity will have to be thoroughly evaluated in CKD patients, and notably the effects of antiFGF23 therapies on immune responses and infection rates should be quantified.

Conclusion and perspectives

Future studies are required to further clarify the impact of FGF23 and vitamin D, as well as their interplay during CKD, on immune cells. In particular, the differential effects of FGF23 on renal and extra-renal 24-hydroxylase expression, as well as potential confounding effects of endocrine $1,25(OH)_2D$ as an inducer of bone FGF23 expression will need to be addressed. Nevertheless, current data indicate that elevated expression of FGF23 may play a crucial role in defining immune responses to vitamin D and this, in turn, may be a key determinant of infections in patients with CKD. These basic data will need to be confronted to epidemiological studies directly focusing on a potential link between FGF23 and infections. Moreover, although therapeutic targeting of FGF23 may be a strategy to delay the onset of secondary hyperparathyroidism and bone and mineral disorders associated with CKD, the effects of such approach on global, cardiovascular and infectious morbi-mortality will also have to be studied.

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