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Short Communication

New Insights into Regulation of FGF23 in Chronic Kidney Disease and its Role in Cardiovascular Disease

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Patients with Chronic Kidney Disease (CKD) have 2.8 to 3.4-fold higher mortality compared to individuals with normal kidney function, mostly attributed to increased risk for Cardiovascular (CV) events [1,2]; however, this increased risk is not fully explained by the traditional CV risk factors such as diabetes, hypertension, hyperlipidemia, smoking etc [1]. Over last decade, Fibroblast Growth Factor-23 (FGF23) has emerged as a strong predictor of CV disease and all-cause mortality in both general and CKD population [3-5]. In this context; however, it is not clear if the relationship of FGF23 with morbidity and mortality is causative or merely associative. Uncertainties also linger about the regulation of FGF23 in CKD patients. Here is the new insight into the role and regulation of FGF23 in CKD.

FGF23 was originally discovered as a phosphaturic hormone. It is produced and secreted by osteoblasts and osteocytes with 1,25(OH)2D as a major direct known stimulus and FGF23 in turn induces phosphaturia by down regulating type IIa and IIc sodium-phosphorus co-transporters on the apical surface of the proximal tubular renal epithelial cells [6]. FGF-23 also down regulates the 1-α-hydroxylase enzyme causing decrease in the active form of vitamin D with resultant decrease in intestinal phosphate absorption. FGF23 exerts these actions by binding to the FGF receptor-Klotho complex in kidney and, thus maintains the phosphorus homeostasis. The various FGF23 activating mutations have known to lead to disorders characterized by hyperphosphaturia, hypophosphatemia, fatigue, bone pain and deformities in face of inappropriately low or normal vitamin D levels. Conversely, loss-of-function FGF23 mutations cause hyperphosphatemia, ectopic calcification, premature aging and death [7].

Regulation of FGF23 in CKD

The blood levels of FGF23 increase very early and progressively in CKD up to 100-fold [8]. However, the mechanisms causing this rise of FGF23 levels remain controversial. Being a phosphaturic hormone, phosphorus retention as a result of CKD is currently considered the main force driving the rise of FGF23 in CKD patients [9]. Nonetheless, it is challenged by newer experimental and clinical research studies where modification of phosphorus exposure does not support the above [10-13]. For instance, FGF23 rises very early well before any abnormality in mineral metabolism is seen in the course CKD [14]. Also, FGF23 predicts worse clinical outcomes independent of serum phosphorous [6] and FGF23 declines inconsistently in CKD patients in response to reduction of dietary phosphorus intake and phosphate binders [11]. Finally, rats subjected to 5/6 nephrectomy displayed high blood levels of FGF23 despite being maintained on a phosphorus-free diet [15], while cultured osteoblasts did not increase the expression of FGF23 mRNA in response to incubation with incremental amounts of phosphorus [13]. These observations suggest existence of phosphorus-independent regulation of FGF23 production in CKD patients [6].

FGF23 and Inflammation

Over last few years, several groups have noted a direct correlation of inflammatory markers such as C-reactive protein, Tumor Necrosis Factor-α (TNF), adhesion molecules and Interleukin (IL)-6 with circulating FGF23 in patients with CKD [16,17], implicating a role of systemic inflammation in the regulation of FGF23. Laboratory research has shown that inflammation reduces expression of Klotho in the mouse kidney, a mechanism toward the development of renal resistance and compensatory rise in blood concentration of FGF23 [18]. We have also recently learned that although the phosphorus binders sevelamer, lanthanum and calcium acetate are similarly capable of lowering serum PTH and fractional renal excretion of phosphorus in stage-3 CKD patients, only sevelamer or lanthanum lowered serum FGF23 [19,20]. Of note, these same 2 phosphorus binders, but not calcium acetate, demonstrate anti-inflammatory properties [21,22]. In this context, I also like to cite the intriguing observation of four-fold increase of circulating FGF23 within days after intravenous

supplementation of iron, since iron infusion causes almost immediate oxidative and inflammatory responses [23,24], we suspect the latter may mediate the effect of iron on FGF23. These observations strengthen the possibility that FGF23 is affected by inflammation. In an early proof of concept study in differentiated mouse osteoblastic cultures, basal Fgf23 mRNA was dose-dependently up-regulated by pro-inflammatory cytokines TNF, IL-1β and TWEAK, and bacterial lipopolysaccaride. Similar effects were observed in human bone samples. TNF- and IL-1β induced Fgf23 expression was NF-κB-dependent [25]. Systemic inflammation is widely prevalent in CKD patients and considered as one of the non-traditional risk factor for CV disease in this population. It is likely that as one of the mediators of the inflammation FGF23 may contribute to this increased CV disease in CKD population.

Role of FGF23

Originally discovered as phosphaturic hormone with main purpose to maintain the phosphorus homeostasis, FGF23 lately has emerged as a prognostic factor in health and disease processes. Since the initial paper by Gutierrez et al. demonstrating higher mortality with increasing levels of plasma FGF23 in dialysis patients [5], many observational studies have reported FGF23 association with rapid progression of CKD, Left Ventricular Hypertrophy (LVH), CV disease and mortality in both general and CKD population [3,4]. Nonetheless, till recently, it was not clear if FGF23 is merely a marker or a mediator of the worse prognosis. In latest animal studies, FGF23 has been directly linked with the development of CV disease. Systemic and intra-myocardial administration of FGF23 for 5 days caused LVH in wild-type mice and 2-week treatment with FGF-receptor blocker attenuated LVH in CKD rats [26], suggesting direct role of FGF23 in CV disease process. However, administration of FGF23-antibody for 6 weeks to 5/6 nephrectomy CKD rats increased mortality [27]. Supporting the latter idea, inactivating mutations of FGF23 in humans is associated with accelerated aging and early mortality [6]. These results suggest that high levels of FGF23 are detrimental; though complete inhibition may even bear worse outcomes. Further studies are required to delineate the exact role of FGF23 in diseases. Interventional studies are underway aiming at reduction of FGF23 by dietary restriction of phosphorus orphosphate binders with the ultimate goal to look at the hard outcomes.

Summary

FGF23 is one of the essential factors to maintain the bone-mineral homeostasis. Recently it has emerged as a strong prognostic marker of CV disease and mortality in general and CKD population. FGF23 levels rise progressively with CKD and associated abnormal phosphorus metabolism is considered the main stimulus of FGF23 synthesis. However, latelysystemic inflammation is getting attention as a regulator of FGF23 synthesis. Nonetheless, this area needs further confirmatory studies. Similarly, more investigations are required before FGF23 is labeled as pathological mediator in the development of CV disease.

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