FGF23: more a matter of the heart than of the vessels?

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In 2008, Gutierrez et al. [1] were the first to demonstrate a very powerful association between FGF23 serum levels and mortality in incident dialysis patients. Meanwhile, the same relationships were confirmed in prevalent dialysis patients, in CKD patients not on dialysis and even in patients with normal renal function [2–5], and to our knowledge no published report has failed to observe FGF23 as a significant risk predictor for hard outcomes including all-cause and cardiovascular mortality or cardiovascular morbidity. Given these uniform associations, the question has arisen, whether FGF23 levels may just reflect the toxicity of phosphate overload in these patient cohorts, or whether FGF23 may harm cardiovascular tissues by intrinsic mechanisms yet to be detailed—Myles Wolf coined the term of FGF23-related ‘collateral damage’ in this context [6].

In their seminal paper in 2011, Faul et al. [7] demonstrated that intravenous and intramyocardial injections of FGF23 injections led to left ventricular hypertrophy (LVH) in rats. Moreover, they chose the classical CKD rat model of 5/6-nephrectomy with the consecutive phenotype of secondary hyperparathyroidism, hyperphosphatemia and hypertension in order to show that despite no change in this ‘clinical’ phenotype the sole administration of a FGF-receptor blocker could fully prevent the development of LVH in this model. While LVH in these experimental settings was found not to be klotho-dependent, it was instead shown that the calcineurin-NFAT pathway was instrumental in this cardiac FGF-receptor signalling.

Several reports also focused on FGF23-associated reactivity and remodelling of the arterial vasculature. Studies in in vitro and in vivo models as well as in humans [8–11] have demonstrated that both phosphate and FGF23 blunt endothelial function. For example, Mirza et al. [11] found a significant association of FGF23 serum levels with impaired vasoreactivity and increased arterial stiffness in a community-based cohort of subjects aged above 70 (n = 967). More recently, a couple of studies evaluated the potential direct impact of FGF23 on vascular calcification processes. Jimbo et al. [12] used both intact aortic rings obtained from uraemic rats and vascular smooth muscle cells in vitro to address this question. Here, FGF23 acted synergistically on the acceleration of phosphate-induced calcification. This effect was shown to be dependent on local expression of klotho in the vessel wall and on activation of the signal transduction pathway ERK1/2. However, in another similar experimental set-up plus in a subcohort of the Chronic Renal Insufficiency Cohort (CRIC) study (n = 1501 CKD patients) no relationships between the occurrence of vascular calcifications and FGF23 levels could be confirmed [13]. This latter setting, however, did rule out intravascular klotho expression, so the question remains under which conditions arterial vessels express klotho, or whether the detection of klotho in the experiments by Jimbo et al. was immanently limited to their individual study design.

Hsu et al. [14] now provide data on the association of FGF23 with relevant surrogates of vascular function in a large patient sample of the Multi-Ethnic Study of Atherosclerosis (MESA) study cohort (n = 5977 patients). The MESA study was initiated in July 2000 to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in a population-based sample of subjects aged 45–84 years, the majority of whom presented with normal renal function [15]. Readouts of vascular reactivity were large (LAE) and small artery elasticity (SAE) measured by pulse contour analysis of the radial artery, pulse pressure measured with an automated sphygmomanometer, and ankle brachial index (ABI) calculated as the ratio of the ankle and brachial systolic blood pressures.

In essence, no associations with arterial stiffness, as measured by pulse pressure, LAE, SAE, or high ABI were demonstrated in this population, confirming previous results by Scialla et al. and Lindberg et al. [13, 16]. Why are these data of importance? Firstly, the MESA study presents by far the largest and best defined study cohort evaluated in this context. Secondly, multiple measures of vascular reactivity were performed which have been proven valuable as independent predictors of outcome in this MESA cohort. However, these results must still leave open the question of whether FGF23 impacts on vascular reactivity in patients with advanced CKD, especially because the absolute range of FGF23 in this predominantly normal population was magnitudes below those levels reached in renal failure.
Given the strong translational data by Faul et al., would it not be obvious to primarily bet on the heart as the predominant target organ of FGF23 than on the peripheral cardiovascular system anyway? Indeed, Scialla et al., recently provided observational evidence again from the well-defined CRIC cohort of CKD patients not on dialysis (n = 3860) [17]. Here, elevated FGF-23 was associated more strongly with chronic heart failure than with atherosclerotic events even after multiple adjustments. Preliminary data from the recent ‘EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events’ (EVALVE) study showed that the magnitude of FGF23 lowering by cinacalcet was associated with an improved cardiovascular outcome of this cohort [18]. Of note, the single hard end point significantly ameliorated by cinacalcet even in the intention-to-treat population in the EVALVE trial was heart failure events [19]. Additional very intriguing, although so far insufficiently explained associations were observed between FGF23 levels and both incident and prevalent atrial fibrillation in the recent past [20, 21] – such findings may suggest the presence of a heart–bone-axis that will have to be elaborated and defined in the future.

With regard to potential collateral cardiovascular damage inflicted by inappropriately high FGF23 levels in patients with or without CKD, a few insights are appearing on the medical horizon. The current report by Hsu et al. indirectly emphasizes that FGF23 appears to be more a myocardial than vascular toxin. Furthermore, there may be a dissociation between the protective physiological phosphatonin effects of FGF23 secretion as a result of phosphate loading, and inherent FGF23 properties which may act on and damage the vessel wall. What we have now are data that in each population, be it with normal, moderately impaired or severely impaired renal function, those subjects with the highest FGF23 levels within their group show the worst cardiovascular prognosis. What we certainly do not have at the moment is the cardiorenal system anyway? Indeed, Scialla et al. recently provided evidence that the phosphatonin effects of FGF-23 might be more of a myocardial than on the peripheral cardiovasculat system [21].

Conflict of Interest Statement

None declared.


REFERENCES


Received for publication: 20.7.2014. Accepted in revised form: 23.7.2014