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COMMENTARY

FGF23 in chronic kidney disease: are we lost in translation?

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Commentary on: Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R *et al.* 'Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial.' *Circulation* 2015; **132**: 27–39.

Fibroblast growth factor 23 (FGF23) is a protein synthesized by osteocytes that has a key role in the 'bone-parathyroid-kidney' axis and the regulation of phosphate/calcium metabolism. Three main effects have been classically described: hypophosphatemia (through an inhibition of phosphate reabsorption in the proximal tubule), decreased PTH levels and decreased 1-25OH_2 levels (through an inhibition of 1α hydroxylase and an activation of 24 hydroxylase activity in the kidney).[1] Off-targets of FGF23 have also been demonstrated, notably on cardiomyocytes,[2] monocytes[3] and osteoclasts.[4] Recently, the effects of FGF23 in the distal renal tubule have been more precisely defined: it stimulates calcium reabsorption through TRPV5,[5] whereas it also stimulates sodium handling and increases blood pressure.[6] In terms of physiology, the links between iron metabolism and FGF23 seem also of importance, although still under investigation.[7]

In human diseases, FGF23 can be deregulated, either in genetic diseases, or in acquired diseases. Four groups can be distinguished: diseases with primary increase in FGF23 levels (for example, hypophosphatemic rickets or tumor-induced osteomalacia), diseases with primary decrease in FGF23 levels (for example, hyperphosphophatemic tumoral calcinosis with decreased intact FGF23 levels but increased C-terminal levels, except in cases of Klotho mutations), diseases with secondary increase in FGF23 levels (for example, chronic kidney disease, CKD) and diseases with secondary decrease in FGF23 levels (for example, VDR deficiency leading to hereditary vitamin D-resistant rickets, hyperphosphatemic tumoral calcinosis owing to Klotho mutations).[8]

A lot of studies have focused on FGF23 during CKD, this biomarker being indeed the first to be deregulated in early CKD. In such a setting, increased FGF23 levels have been shown to be a risk factor for cardiovascular mortality, general mortality, progression of renal disease, resistance to vitamin D analogs and more recently infections.[9–12] In healthy volunteers, oral phosphate loading increases FGF23 levels, whereas it is the contrary for dietary phosphate restriction. FGF23 levels increase progressively as the renal function declines, well before the onset of a critical reduction in the nephron number. However, the early increased FGF23 levels during CKD are observed well before increased phosphate/PTH or decreased 1-25OH_2 levels, and the exact mechanisms and triggers of this increase remain mysterious: it could be secondary to a decreased renal clearance of FGF23, a compensatory mechanism in an attempt to excrete the excess serum phosphate and keep serum phosphate within the normal range, a response to the treatment with active vitamin D analogs, a compensatory mechanism to the loss of the kidney-secreted Klotho protein and/or an increased production of FGF23 in bone cells.[13]

It remains to be determined in 2015 whether and how decreasing FGF23 levels could improve overall mortality in CKD patients. Indeed, the current standard therapies affect FGF23 levels differently. Briefly, dietary restriction may decrease FGF23 levels; non-calcium-based binders appear to reduce FGF23 levels, whereas calcium-based binders seem to either increase or have no effect on FGF23 levels; finally, active vitamin D sterols increase FGF23 levels, whereas calcimimetics decrease FGF23 levels.[14] Theorically, the use of antiFGF23 agents in CKD could be of interest, but results from animal models have been disappointing, enabling the correction of hyperparathyroidism, whereas increasing phosphate levels and mortality.[15] Anyway, FGF23 antibodies should not be trashed by physicians as the revolution in the field of genetic hypophosphatemic rickets will consist in a near future of using antiFGF23 antibodies.[16] With all these data in mind, the appropriate therapy in CKD that will minimize the rise in FGF23 and most importantly prevent cardiovascular morbidity remains to be defined.

In that setting, two clinical trials evaluating the role of the calcimimetic cinacalcet were performed in patients with CKD. The ADVANCE trial provided evidence that cinacalcet combined with low doses of vitamin D may slow down the progression of coronary artery calcifications compared with

therapy using larger, varying doses of vitamin D.[17] However, the EVOLVE trial, including 3883 hemodialysis patients with moderate-to-severe hyperparathyroidism randomized either to cinacalcet or placebo and followed-up to 64 months, did not meet its clinical primary end point (time to all-cause mortality, myocardial infarction, hospitalization for unstable angina, heart failure or a peripheral vascular event) using an unadjusted intention-to-treat analysis, although secondary and sensitivity analysis suggested a beneficial effect.[18] However, after pre-specified adjustment for baseline characteristics, patients randomized to cinacalcet experienced a nominally significant 13% lower adjusted risk (95% confidence interval (CI): 4–20%) of the primary composite end point. One main issue of this important clinical trial was the extensive non-adherence, thus leading the intention-to-treat analysis quite challenging.[19]

Secondary analyses of the EVOLVE study were recently published. Cinacalcet decreased the risk of death and major cardiovascular events in older, but not younger (threshold of 65 years of age), patients.[20] Clinical fractures were observed in 255 of 1935 (13.2%) patients randomized to placebo and 238 of 1948 (12.2%) patients randomized to cinacalcet. After adjustment for baseline characteristics and multiple fractures, the relative hazard (cinacalcet versus placebo) was 0.83 (95% CI: 0.72–0.98). Fracture rates were higher in older compared with younger patients, and the effect of cinacalcet appeared more pronounced in older patients.[21] However, most importantly, a secondary analysis including 2602 patients (out of the initial 3883) with samples at both baseline and week 20 showed that a significantly larger proportion of patients randomized to cinacalcet had $\geqslant$30% reductions in FGF23 levels (68 versus 28%). Among patients randomized to cinacalcet, a $\geqslant$30% reduction in FGF23 between baseline and week 20 was associated with a nominally significant reduction in the primary composite end point (relative hazard, 0.82; 95% CI: 0.69–0.98); results were similar for cardiovascular mortality, sudden cardiac death and heart failure. Thus, in addition to significantly lower FGF23 levels, the treatment-induced reductions in serum FGF23 using cinacalcet are associated with lower rates of mortality and major cardiovascular events.[22] This observation appears to be independent of demographic factors and comorbid conditions, reductions in serum PTH, calcium or phosphate and the cumulative dose of vitamin D sterols.[22]

It is now well admitted that FGF23 and cardiovascular status are intimately and strongly associated, but the question has arisen from epidemiological studies to understand whether FGF23 was a direct culprit or only a bystander. Faul *et al.*[2], in their 2011 seminal paper, have well shown that one of the main explanations of FGF23 effects on the cardiovascular system was the left ventricular hypertrophy induced by FGF23. However, the single-pass trans-membrane Klotho protein, well known for its biological properties *in vivo* to enhance FGF23-mediated receptor activation, has mineral effects by itself (increased calcium reabsorption because of a direct modification of the sugar chains of TRPV5 in the distal tubule and direct regulation of PTH synthesis) and also cardiovascular effects.[23] Indeed, low Klotho levels (isolated or secondary to high uremic toxins levels) have been shown recently to be associated with left ventricular hypertrophy in murine models of CKD.[24,25] Independent of this FGF23/Klotho/left ventricular hypertrophy axis, several reports have also shown that FGF23 was also able to blunt the endothelial function and to synergistically accelerate phosphate-induced vascular calcifications. However, other reports have been more controversial, raising the concept that maybe the heart would be the predominant target organ of FGF23, whereas the peripheral cardiovascular system would not be impacted that much by FGF23.[26]

In conclusion, the secondary analyses of the EVOLVE study show that decreasing FGF23 levels may become an important target in the clinical management of CKD patients; however, we should not forget that other therapeutic options such as FGF-R modulation are currently under evaluation,[27] and that, last but not least, increasing Klotho levels may also become a promising tool for cardiovascular outcomes and overall mortality. For daily clinical practice, let us try to keep serum phosphate within the normal range.

Conflict of Interest

JB received research grants from Amgen, Sandoz and Crinex, and also received consulting and lecture fees from Amgen, Genzyme and Pfizer.

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