CKD-MBD

EDITORIAL COMMENT

Where is the link between mineral bone markers and cardiovascular disease in CKD?

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In the manuscript by Di Lullo *et al.* [1], the authors evaluate the association between cardiac valve calcification extent and biochemical markers of mineral metabolism and inflammation, such as parathyroid hormone (PTH), phosphate (P), calcium (Ca), fibroblast growth factor 23 (FGF23), Klotho, vitamin D and C-reactive protein, in a population of incident chronic kidney disease (CKD) stage 3–4 patients. Interestingly, in the multivariate analysis, high serum PTH and FGF23 levels associated with aortic valve calcification. Authors' conclusions are that further studies 'should examine whether FGF23 assay should be included in routine clinical evaluation of CKD, as part of CV risk stratification'. How far away are we from suggesting routinely screening for FGF23 in the CKD population?

CKD patients have a dramatically higher incidence of cardiovascular morbidity and mortality compared with the general population [2]. In the last 10 years, several studies have pointed out that vascular calcification is a major cause of cardiovascular disease in the dialysis population. In CKD patients, high levels of plasma Ca, serum P, PTH and FGF23 play a critical role in the pathogenesis of cardiovascular events [3].

Patients develop extensive medial calcification, which causes increased arterial stiffness and high morbidity and mortality due to cardiovascular events [4, 5]. A variety of risk factors are associated with vascular calcification in dialysis patients (time on dialysis, uraemic toxins, history of diabetes and inflammation), but abnormalities in bone mineral metabolism may play a critical role [6]. In fact, elevated serum P, Ca–P product, PTH and FGF23 levels contribute to vascular calcification, although their roles are incompletely understood [7, 8]. Elevations of serum P and Ca–P product levels may worsen cardiovascular events in the uraemic population, through a progressive increase in Ca deposition in the coronary arteries and heart valves [9].

Recent insights into novel roles of bone biomarkers, such as FGF23, in vascular biology make this primarily kidney-derived protein a possible candidate to form a link between bone and cardiovascular morbidity and mortality [10]. A central aspect of FGF23 and α-Klotho is regulation of their expression and the apparent disconnect between tissue level and concentration in blood. FGF23 is regulated by several feedback loops consistent with endocrine systems: it reduces serum P, 1,25-dihydroxyvitamin D and PTH, and these factors stimulate FGF23 expression in bone. Active vitamin D is the most potent regulator of FGF23 and acts directly on FGF23 gene transcription by binding a vitamin D-responsive element in the gene promoter region [11].

FGF23 is now considered a major determinant of circulating levels of P and vitamin D metabolites. This role is accomplished by regulation of the expression of transmembrane P carriers and by modulating activity of the hydroxylases that activate or catabolize vitamin D. All of these FGF23 effects are obtained through activation of specific receptors. Significantly, however, the presence of a co-receptor is essential. Intriguingly, this co-receptor, Klotho, besides contributing to FGF23 actions, also has specific biological effects that may be relevant for cardiovascular disease in CKD.

Several small clinical studies report on the association between higher levels of FGF23 and vascular calcification. Increased serum levels of FGF23 have been recognized as a risk factor for mortality either in conservative or in maintenance haemodialysis populations [12, 13]. Recently, a prospective study of patients with CKD stages 3–5D, with a follow-up of 35 ± 3 months, showed

a significant positive correlation between serum FGF23 levels and coronary calcification (CAC) score, with a 62.5% sensitivity and a 75.9% specificity. In this study, regression analysis identified FGF23 levels together with severe CAC (>400) as independent risk factors for all-cause mortality [14]. Cardiac valve calcification is a common finding in CKD with a high rate of cardiovascular mortality [15].

Even if in the preclinical setting the role of FGF23 in vascular calcification pathogenesis is still unclear, interestingly, high FGF-23 levels were independent predictors of mitral valve calcification and a risk factor for cardiovascular mortality in 150 diabetic patients with mild to moderate CKD [16]. A relevant contribution on the possible pathogenetic role of FGF23 in the development of cardiovascular disease in renal patients comes from the work by Faul *et al.* [17]. In this study, increased levels of FGF23 were independently associated with left ventricular hypertrophy (LVH) in a large CKD population. Importantly, with *in vivo* experimental data, LVH was induced by an intramyocardial or intravenous injection of FGF23 in wild-type mice. LVH developed also in transgenic Klotho-deficient mice with mildly elevated FGF23 levels. Finally, in *ex vivo* studies (isolated cardiomyocytes), these authors demonstrated a direct hypertrophic effect of FGF23 through interaction with an FGF receptor that activates the calcineurin–nuclear factor of activated T-cells signalling pathway, independently of the presence of the co-receptor Klotho. In an established animal model of CKD, treatment with an FGF receptor blocker attenuated LVH, with no significant change in blood pressure. All of these data point to a causal role for FGF23, which seems to be Klotho-independent, in the pathogenesis of LVH. Accordingly, chronically elevated FGF23, as described in CKD, could directly contribute to LVH and high rates of cardiovascular mortality in these patients [17].

Lower levels of FGF23 resulting from therapies aimed at controlling CKD-MBD were associated with lower rates of cardiovascular events [18]. The clinical significance of FGF23 as a biomarker of CKD-MBD or of cardiovascular risk in renal patients is thus waiting for definite settlement.

Besides FGF23, also its co-receptor Klotho is now widely investigated for potential involvement with cardiovascular disease through direct or indirect mechanisms. Available data indicate the strict pathophysiological link existing between FGF23 and Klotho. Even very early reduction in renal function associates with reduced circulating levels of Klotho (which is mainly produced by the kidney). It is currently accepted that this reduction prompts an increment of FGF23 secretion tentatively aimed at balancing the peripheral resistance secondary to reduction of the co-receptor. As a result, it may well be that at least some of the cardiovascular disease of CKD is secondary to reduced Klotho systemic activity. In fact, Klotho exists in a membrane-bound form and a soluble form (s-Klotho). Transmembrane α-Klotho (TM-Klotho), expressed in renal tubules, is mainly regarded as the cofactor for FGF23 receptor. Circulating soluble α-Klotho (s-Klotho) results from TM-Klotho shedding and is regarded as the component of Klotho that is responsible for its systemic, specific and FGF23-independent effect. Decreased TM-Klotho expression, described in both experimental and human CKD, lowers FGF23 effects on kidney tubules, but also lessens circulating s-Klotho [19]. In CKD patients, circulating s-Klotho is lower than normal and its reduction is detectable from CKD stage 2. s-Klotho positively correlates with eGFR, but also with serum Ca and, negatively, with serum P, PTH and FGF23. In this setting, serum levels of FGF23 are also higher than normal, with increments detectable from CKD stage 2. Assuming that s-Klotho mirrors TM-Klotho synthesis, low-circulating s-Klotho somehow describes the ensuing tubular resistance to FGF23, which, accordingly, is increased as a secondary response [20]. Thus, levels of s-Klotho can be regarded as an early marker of CKD-MBD, but more reliability of current assays for s-Klotho is needed.

In conclusion, since FGF23 is reliably measured in serum or plasma, a wealth of epidemiological studies have explored cross-sectional and longitudinal relationships between FGF23 and clinical outcomes. The outcome of these studies unequivocally points to FGF23 as a robust marker of disease surrogate markers as well as hard clinical end points including mortality and cardiovascular events. Such relationships should be confirmed in CKD patients as well as in community-dwelling adults and in populations with a high occurrence of pre-existing cardiovascular disease.

Conflicts of interest statement

None declared.

(See related article by Di Lullo *et al.* Fibroblast growth factor 23 and parathyroid hormone predict extent of aortic valve calcifications in patients with mild to moderate chronic kidney disease. *Clin Kidney J* (2015) 8: 732–736.)

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