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Review

Phosphate and FGF23 in the renoprotective benefit of RAAS inhibition

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ABSTRACT

Renin angiotensin-aldosterone system (RAAS) blockade is a mainstay of chronic kidney disease (CKD) treatment given its beneficial effects on proteinuria, nephroprotection, heart disease and global mortality.

The FGF23/Klotho/phosphate axis is crucial for phosphate excretion. During CKD, loss of Klotho, decreased phosphate excretion and FGF23 elevation are early events contributing both to renal disease progression and to cardiovascular complications. Experimental evidence suggests that Klotho replacement may improve renal and cardiovascular disease during CKD.

Recent evidence suggests that both RAAS activation and proteinuria decrease Klotho expression and lead to phosphate retention and FGF23 elevation. In opposition RAAS blockade may reverse Klotho loss during CKD in both experimental and human studies, with direct and indirect expected beneficial effects on the kidney and cardiovascular system. This effect of RAAS blockade on the FGF23/Klotho/phosphate axis may participate in explaining some of the beneficial effects of these drugs during CKD.

In this article we review the evidence linking RAAS blockade to modulation of the FGF23/Klotho/phosphate axis and the beneficial effects of these regulations.

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1. Introduction

ACE inhibitors and AT1 receptor Blockers (ARBs) display renoprotective effects in proteinuric diabetic and nondiabetic kidney diseases. Renin-angiotensin-aldosterone system (RAAS) blockade reduces proteinuria by decreasing intraglomerular pressure via a vasodilatory effect on the afferent and efferent glomerular arterioles [1]. This effect is significant (average 30%) and independent of the cause of proteinuria. ACE inhibitors' and ARB's nephroprotective properties on long term renal function have been demonstrated in several populations of proteinuric chronic kidney disease (CKD) [2–6] patients. In addition these drugs increase survival and improve heart function during left ventricular dysfunction [7–10]. Finally, RAAS blockade has been recently associated to decreased mortality in patients with CKD [11]. The FGF23/Klotho system regulates phosphate excretion and plays a major role in mineral metabolism [12]. Alterations of mineral metabolism are early events in CKD and contribute both to renal disease progression and to CKD extrarenal complications (mostly cardiovascular). Both proteinuria and RAAS have been described to interact with the FGF23/Klotho/phosphate system. In this article, we first introduce the FGF23/Klotho/phosphate system in CKD, then review the evidence linking proteinuria and RAAS to the FGF23/Klotho system and finally discuss the potential beneficial role of RAAS inhibition via FGF23/Klotho and phosphate regulation.

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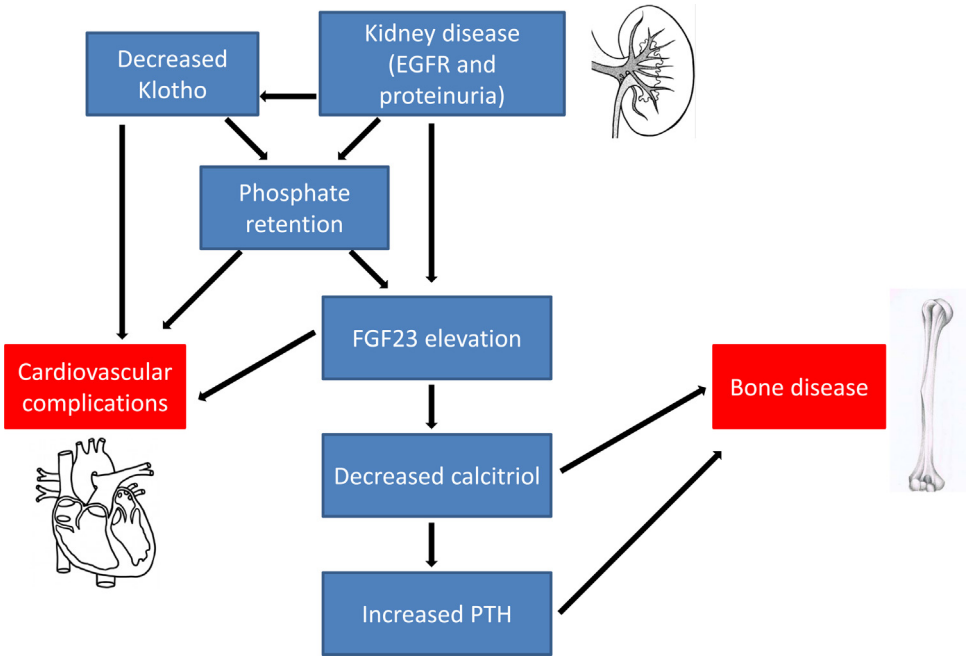

Fig. 1. Schematic simplified overview of mineral metabolism adaptations during chronic kidney disease.

2. The FGF23/Klotho/phosphate axis during chronic kidney disease (CKD)

Major modifications of the FGF23/Klotho/phosphate axis occur already early in the course of CKD and influence both renal and extrarenal evolutions of the disease [13,14]. The anomalies of phosphate excretion are usually defined as CKD-mineral and bone disease (CKD-MBD). In general, the more advanced the CKD, the more severe the CKD-MBD. Epidemiologically, there are clear evidence linking perturbations of mineral metabolism to cardiovascular mortality and renal disease progression. Phosphatemia is indeed predictive of cardiovascular mortality both in patients with altered or preserved renal function, even when phosphate levels are still within the normal range [15–20]. Phosphate retention may also directly enhance CKD progression [21,22]. FGF23 elevation is a marker of increased mortality in several population including CKD patients, kidney allograft patients, dialysis patients and the general population [23–28]. FGF23 levels are predictive of renal function decline in CKD patients [26]. Klotho measurements are not highly reproducible in human currently and large epidemiological studies linking its expression to cardiovascular or renal prognosis are lacking, but experiments clearly point to a key role of this protein in mediating cardiovascular and renal protection [14,29–35].

The pathophysiology of CKD-MBD is still a matter of debate. The current understanding of CKD-MDB is that Klotho loss is a very early event in different types of CKD [13,14,36–38]. Klotho is a transmembranous protein expressed mainly in the distal nephron, and at lower levels in other segments of the nephron and the parathyroid gland [13,14]. Klotho was first identified as an anti-aging protein and its complete deletion in mice induces early mortality with a multisystemic disease including massive cardiovascular calcifications, bone disease, skin atrophy and lung emphysema among others [39]. Targeted renal Klotho deletion induces an extrarenal phenotype similar to that observed in the Klotho null mouse, indicating the major importance of renal Klotho in the cardiovascular calcifications and phosphate retention of Klotho deficient animals [40,41]. Vascular calcifications of Klotho null mice can in part be rescued by lowering phosphate retention through different interventions, which also improve lifespan, demonstrating that phosphate accumulation is as an important factor in this cardiovascular phenotype [42]. Indeed Klotho is a co-factor for FGF23, a major phosphaturic hormone produced in the bone [12], and its presence is mandatory for FGF23 binding on its receptor and being biologically active. In addition, soluble Klotho directly acts on some phosphate and calcium transporters and induces phosphaturia [43]. Klotho loss therefore impairs phosphate excretion and has major detrimental effects through this pathway given the vascular, an potential renal, toxicity of phosphate [44,45]. In addition, Klotho loss may have phosphate independent effects [14,29]. Experimentally Klotho replacement rescues the progression of nephropathies [33,34,46]. This effect may be mediated by several mechanisms among which the repression of the Wnt/β-Catenin profibrotic signaling pathway by Klotho may play an important role [35]. Finally, during experimental CKD, soluble Klotho administration protects against CKD associated cardiovascular complications [31,32]. This likely relies on the phosphaturic properties of Klotho, but also on direct antifibrotic properties of the protein, via regulation of the cardiac Smad pathway for example [29].

During CKD, circulating and renal Klotho decrements precedes FGF23 elevation [47,37]. The mechanisms underlying exaggerated FGF23 secretion in CKD are not known. Increased FGF23 secretion may be consecutive to Klotho loss or to a transient positive phosphate balance due to GFR loss [12,48]. Alternative explanation for the high FGF23 levels of CKD may be an exaggerated secretion by bone cells via unknown factors, or FGF23 secretion by diseased kidneys [49,50]. FGF23 then stimulates phosphate excretion and decreases 1.25 vitamin D hydroxylation, maintaining phosphatemia until late stages of CKD, and potentially even decreasing it at initial stages [51]. PTH secretion is then stimulated by the decreased levels of 1.25 vitamin D [52]. Maintenance of a near-normal phosphatemia in advancing CKD therefore results from the elevation of phosphaturic hormones. It is however likely that phosphate body stores increase in a much faster way than phosphatemia during progressive CKD [48], although no clear demonstration of this exists since no reliable measurements of phosphate stores are available. One of the explanations for the excellent predictive value of FGF23 levels for vascular complications in CKD may therefore be