



Editorial

Is Klotho deficiency independently associated with cardiovascular risk in chronic kidney disease?



Patients with chronic kidney disease (CKD) suffer from a high burden of cardiovascular disease (CVD) [1]. This is partly due to progressive deterioration of calcium–phosphate homeostasis. Although the molecular mechanism of action of Klotho is not well understood, fibroblast growth factor-23 (FGF-23) and its coreceptor Klotho have emerged as pivotal players in calcium–phosphate homeostasis. Klotho was first identified in mice, where mutations of the gene led to a syndrome resembling premature aging [2]. The Klotho protein exists in both a membrane bound and a soluble form (sKlotho). sKlotho is derived from the extracellular part of membranous Klotho through alternative splicing of the Klotho gene and has a unique role in renal calcium and phosphate excretion independent of FGF-23 [3]. There is growing interest in using sKlotho as an important biomarker of kidney function, based largely on studies showing that blood and urine concentrations of sKlotho decrease early in the course of CKD [4,5].

In addition, sKlotho has also been explored for a potential biomarker for CVD. In this issue, Abdallah et al [6] investigated the association between sKlotho and CVD risk in hemodialysis patients. They measured sKlotho and FGF-23 in 88 regular hemodialysis patients and 28 normal populations (control group), using a commercially available enzyme-linked immunosorbent assay. For evaluation of CVD, carotid intimal-media thickness and left ventricular (LV) dysfunction were estimated by ultrasonography. The sKlotho level was significantly low in hemodialysis patients compared to controls, and FGF-23 was significantly high in hemodialysis patients compared to controls. The concentrations of parathyroid hormone, FGF-23, and phosphate were significantly higher when the Klotho level was lower (< 476 pg/mL, $n = 44$). In contrast, serum calcium was significantly lower when the sKlotho level was lower. Notably, the prevalence of coronary artery disease (CAD) was higher in patients with a lower sKlotho level. Regression analysis of sKlotho for the relationship with different markers of CVD revealed that sKlotho was significantly associated with carotid intimal-media thickness, LV ejection fraction, and CAD. However, these data have some limitations. Data on dietary phosphate intake, a known determinant for both serum phosphate and FGF-23 levels, were not collected. Because sKlotho has a circadian variation, measurement at fixed time is necessary [7]. Similarly, a reduced Klotho level was associated with the presence and severity of

CAD [8]. On the other hand, sKlotho was not independently associated with CVD in a population of dialysis patients [9]. Buiten et al [9] evaluated the association between sKlotho and cardiovascular outcomes in dialysis patients, showing that patients with a lower sKlotho (< 460 pg/mL) were associated with more CAD and LV dysfunction. After adjusting for confounders, however, sKlotho was not independently associated with the presence of CVD.

Despite mixed results of sKlotho level and CVD risk from clinical studies, most animal study results support that Klotho deficiency is associated with CVD risk. Klotho deficiency in mice resulted in hyperphosphatemia, hypervitaminosis D, hypercalcemia, arteriosclerosis, and ectopic calcification including vascular calcification [2,4]. Transgenic CKD mice overexpressing Klotho had better kidney function, enhanced phosphaturia, and less soft tissue calcification as compared with wild-type mice with CKD [4]. Interaction of Klotho with FGF-23 receptor leads to phosphaturia because of the inhibition of sodium-dependent phosphate cotransporter type IIa in the brush-border membrane of proximal renal tubular cells. Independent from FGF-23, soluble urinary Klotho has been found to directly regulate the phosphate transport. In the proximal tubule of the kidney, it promotes internalization of sodium-dependent phosphate cotransporter type IIa by deglycosylation [4]. These effects of Klotho on urinary phosphate excretion probably contribute to its inhibitory effects on calcification.

In brief, recent studies suggest that sKlotho deficiency should be a good explanation for the high risk of CVD in CKD. However, further studies are required to demonstrate whether sKlotho is just a biomarker or a predictor of CVD in CKD and dialysis patients.

Conflicts of interest

The author has no conflicts of interest to declare.

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