Fibroblast growth factor 23 (FGF23), a hormone involved in mineral metabolism regulation, may be more important in chronic kidney disease (CKD) and cardiovascular disease (CVD) than previously believed. Recent insights into FGF23 have led to advancement in interpreting CKD and CVD progression data, ascribing to FGF23 a pivotal role in these pathologies independent of its co-receptor klotho. Stefanie Krick, M.D., Ph.D. and her research colleagues examined the current experimental and clinical evidence regarding the role of FGF23 in physiology and pathophysiology of CKD and its associated complications with an emphasis on CVD.

In this study, Krick and her fellow researchers found an impressive monotonic increase in the rate of death in a nested case–control sample of patients. In these patients, serum levels of FGF23 were up to a thousand times higher than normal. In this large cohort of patients, higher quartiles of FGF23 were associated with an increased risk of mortality and also of entering renal replacement therapy.

In patients with CKD, serum levels of FGF23 rise progressively as kidney function declines. This response is mainly a compensatory mechanism to maintain neutral phosphate balance by promoting additional urinary phosphate elimination to counteract the defect in renal excretory capacity. CKD is also associated with impaired host response, increased susceptibility to infections, and systemic inflammation. Interestingly, klotho, a transmembrane protein, which also exists in a soluble form, has recently been described as the co-receptor of FGF23 and is downregulated in kidney disease. It has also been demonstrated that klotho is reduced in COPD patients and protects the alveolar epithelium against oxidative damage.

FGF23 seems to function as a circulating factor that can directly contribute to cardiac hypertrophy, inflammation, and impaired host response in CKD. Novel laboratory methods must be developed to reliably assess klotho levels in patients as well as klotho and FGF23 activity in vitro and in experimental in vivo settings. Extending knowledge of FGF23-FGFR biology in the context of CKD and systemic inflammation will eventually lead to the identification of novel drug targets and the development of pharmacological interventions that ultimately might reduce the burden of cardiovascular and pulmonary injury, decrease systemic inflammation, prevent infections, prolong kidney transplant survival, and ultimately decrease mortality among the millions of CKD patients worldwide.