Fibroblast Growth Factor 23 in Autosomal Dominant Polycystic Kidney Disease

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Fibroblast growth factor 23 (FGF23) is a 23-kDa protein that is synthesized in bone mainly by osteocytes and less in the spleen and brain, which has a key role in the "bone-kidney/parathyroid" axis and most importantly regulating serum phosphate and calcium. Fibroblast growth factor 23 acts mainly as a phosphaturic factor and a suppressor of 1α-hydroxylase activity in the kidney. Moreover, it also inhibits 1α-hydroxylase activity whereas it stimulates the 24-hydroxylase activity, thus leading to a decreased 1,25-dihydroxyvitamin D serum level.[1] These two pathways account together for the hypophosphatemic effect of FGF23. Fibroblast growth factor 23 indirectly mediates secretion of parathyroid hormone (PTH) and also has a direct effect on the parathyroid gland to suppresses PTH synthesis and secretion. However, PTH induces expression and secretion of FGF23 both directly and indirectly.[2] Fibroblast growth factor 23 can stimulate local expression of 1α-hydroxylase in the parathyroid gland, suggesting that it can also indirectly downregulate PTH synthesis through an increased local production of calcitriol.

For its effects on the kidney, FGF23 requires Klotho. Basically, FGF23 binds to the Klotho and suppresses renal tubular phosphate reabsorption and 1α-hydroxylase activity. Markedly elevated circulating FGF23 levels are found in patients with advanced chronic kidney disease (CKD).[3] In these patients, the elevation of serum FGF23 levels is associated by the retention of phosphate, increase in PTH secretion, and a reduction in 1,25-dihydroxyvitamin D levels. Fibroblast growth factor 23 levels are independently associated with progression of CKD and development of cardiovascular events and mortality. However, the rise in serum FGF23 in patients with CKD precedes or follows the reduction in glomerular filtration rate (GFR) remains a matter of debate. Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder characterized by bilateral growth of numerous cysts between ages 20 and 40 years. The cysts replace approximately 50% of the normal parenchyma. Autosomal dominant polycystic kidney disease is a slowly progressive disease. However, despite the presence of numerous cysts in both kidneys, GFR remains preserved up to the age of 40 years in most patients, because glomerular hyperfiltration of functioning nephrons compensates for the ongoing loss of functional renal tissue.[4-6] Plasma FGF23 concentration increases early, before the clinical decline of kidney function. Fibroblast growth factor 23 was markedly elevated in ADPKD patients compared with GFR-matched CKD patients, and was associated with an apparent renal phosphate leak, while PTH and vitamin D metabolite levels remained in the normal range.[7] Thus, FGF23 was substantively elevated in ADPKD patients compared to other CKD patients matched for GFR, and was associated with increased renal phosphate excretion.[7] Pavik and colleagues[7] showed that ADPKD patients with CKD stage 1 and 2 have 4-fold elevated levels of serum FGF23, whereas PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels remained in the normal range. They demonstrate that in ADPKD patients FGF23 levels are inappropriately high for the degree of severity of renal insufficiency, which relates to renal phosphate leak and consequently leads to low serum levels of phosphate. Also, this study suggests that the high levels of FGF23 in ADPKD patients are specific to that disease.

It seems FGF23 also expresses in the liver, and thus may alter the metabolism of FGF23.[7] Fibroblast

growth factor 23 rises in patients with CKD stages 2 and 3, but in patients with ADPKD, the increase of FGF23 have seen in the early phase of CKD. Patients with ADPKD who have an estimated GFR of 60 mL/min/1.73 m^2 have strongly elevated FGF23 levels, but only a small fraction of these patients present with hypophosphatemia. In ADPKD patients with normal renal phosphate handling, despite high FGF23 levels, reduced soluble Klotho levels were found. However, the rising FGF23 in ADPKD, the mechanisms underlying resistance to the biological actions of FGF23, and the source and cause of the elevated FGF23 levels remained unclear.

Spichtig and colleagues[8] found a 10-fold elevated FGF23 level in ADPKD animals and resistance of the target organs to its biological actions at an early stage of polycystic kidney disease. They showed that excessive FGF23 plasma levels in ADPKD resulted from increased formation of cell lining of the renal cysts rather than from production in bone. In this study, calcium and phosphate levels, renal phosphate transporters, Klotho, and vitamin D remained normal despite increase in plasma FGF23 levels. This may indicate the resistant effect of FGF23 in polycystic kidney disease.[8] Pavik and colleagues found reduced biologic activity of FGF23 in patients with ADPKD that is characterized by low renal phosphate excretion in the setting of increase FGF23 levels. Loss of Klotho and increase in FGF23 are associated with the loss of GFR in patients with ADPKD and may be early markers of the kidney disease in ADPKD.[9] This finding was associated with low serum Klotho levels, suggesting that the resistance to the phosphaturic effect of FGF23 could be mediated by a reduction of Klotho.

Endothelial dysfunction occurs in very early stages of CKD. Endothelial dysfunction is a systemic pathological condition which can result from an imbalance between the actions of vasorelaxing and vasoconstrictor factors. The imbalance is mainly caused by reduced nitric oxide bioavailability or increased generation of reactive oxygen species. Although the major expression of Klotho is in the kidney, parathyroid gland, and choroid plexus, Klotho is expressed in human vascular tissue too. Both Klotho and FGF23 have major roles in the regulation of vascular tone. Klotho overexpression improves endothelial function through increased nitric oxide production tone.[10] Six and colleagues showed that Klotho induced a direct dose dependent vasoconstriction.[11] These findings are compatible with the hypothesis which FGF23 has Klotho-independent effect on vascular tissue, and the mechanism of action of FGF23 may differ from one type of tissue to another.[11] The importance of the cardiovascular effects of FGF23 excess and their independence of the Klotho coreceptor have recently been questioned in patients with a broad range of kidney function impairment. Klotho and FGF23 concentrations combined can induce endothelial cell dysfunction but the correction of Klotho deficiency alone may not be sufficient. In patients with CKD, a strong association has been found between increased serum FGF23 and mortality risk, possibly via enhanced atherosclerosis, vascular stiffness, and vascular calcification. Fibroblast growth factor 23 induced contraction of phosphate in contracted vessels and increased reactive oxygen species production. Phosphate, Klotho and FGF23 together induced no change in vascular tone despite increased reactive oxygen species production. The three compounds combined inhibited relaxation despite increased nitric oxide production, probably duo to concomitant increase in reactive oxygen species production. Although phosphate, soluble Klotho and FGF23 separately stimulate aorta contraction, Klotho mitigates the effects of phosphate and FGF23 on contractility via increased nitric oxide production, thereby protecting the vessel to some extent against potentially noxious effects of high phosphate or FGF23 concentrations. This novel observation indicates that Klotho deficiency is harmful while Klotho sufficiency is protective against the negative effects of phosphate and FGF23 which are additive.

In this issue of the Iranian Journal of Kidney Diseases, Yildiz and coworkers report their study that found markedly elevated FGF23 levels in both hypertensive and normotensive ADPKD patients with normal kidney function. Arterial compliance significantly decreased in early ADPKD patients regardless of hypertension. Also, there was no correlation between FGF23 levels and arterial dysfunction.[12] Several studies reported strong association between FGF23 and cardiovascular risk factors. High levels of FGF23 were associated with endothelial dysfunction in CKD stages 3 and 4 and in an older non-CKD population. In addition, higher FGF23 is associated with left ventricular

hypertrophy, which is an important mechanism of congestive heart failure and arrhythmia and mortality in CKD. In Lindberg and colleagues' study, arterial Klotho expression was low or absent and did not mediate vascular FGF23 signaling in mice.[13] Furthermore, vascular calcification and function were unaffected by FGF23, thus not supporting direct vascular effect of FGF23 as the cause of vascular pathology in CKD. However, interaction between kidney disease, FGF23 release and activity, mineral metabolism, vascular calcification, and cardiovascular disorders are complex. Small sample sizes and different confounding factors limit this conclusion. Hence, we need additional studies to evaluate the true effect of FGF23 in ADPKD patients with preserved kidney function.

CONFLCIT OF INTEREST

None declared.

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