

FGF23 and vitamin D status in CKD

Takayuki Hamano

Department of Comprehensive Kidney Disease Research (CKDR),
Osaka University Graduate School of Medicine

We found that proteinuria of 2+ or greater by dipstick test was associated with low vitamin D status due to urinary loss of 25-hydroxyvitamin D (25(OH)D). Moreover, active vitamin D or its analogues decrease proteinuria. Given our finding that maxacalcitol does not repress renin, the reduction of proteinuria by this agent is attributed to direct upregulation of nephrin and podocin in podocytes, markers of epithelial cells. Therefore, vitamin D seems to block epithelial-mesenchymal transition (EMT). In fact, this agent downregulates a mesenchymal marker desmin in podocyte and block TGF-beta autoinduction, leading to the attenuation of renal fibrosis in unilateral ureteral obstructive (UUO) model. This blockade of EMT might explain our finding that vitamin D prescription in renal transplant recipients was associated with lower incidence of cancer.

Another important molecule is fibroblast growth factor 23 (FGF23). Animal studies revealed that FGF23 itself induces cardiomyocyte hypertrophy through activating the calcineurin-NFAT pathway and enhances cardiac contractility by increasing intracellular calcium levels. In fact, elevated FGF-23 in CKD was associated more strongly with congestive heart failure than with atherosclerotic events including myocardial infarction. Recent findings showed that some iron preparations including iron-based phosphate binders such as ferric citrate reduce serum intact FGF23 levels. We also confirmed that PA-21 decrease this levels. This FGF23 lowering effect of iron prescription might explain the results of FAIR-HF and COFIRM-HF showing the clinical benefit of ferric carboxymaltose in patients with heart failure and iron deficiency.

We also reported that low vitamin D status and high FGF23 levels predicted worse renal outcome. However, administration of massive 25(OH)D exacerbates renal fibrosis in UUO kidney in 1 α -hydroxylase knockout mouse. Moreover, FGF23 inhibits 1 α -hydroxylase in proximal tubules and monocytes. Taken together, it should be not 25(OH)D but local 1,25(OH)₂D that protect the kidney.