The most well-known function of the vitamin D endocrine system is maintaining calcium and phosphorus homeostasis, but studies in the past decades have unveiled a wide range of activities for vitamin D that extends beyond the regulation of calcium and phosphorus metabolism. Those activities include regulation of renal and cardiovascular functions and modulation of immune responses through the renin-angiotensin system (RAS) and the nuclear factor (NF)-κB pathway.

The kidney has a key role in vitamin D metabolism. It not only provides the enzymatic system for the synthesis of 1,25(OH)2D, but also is involved in the uptake of filtrated 25(OH)D from urine in the form of vitamin D-binding protein (DBP)-25(OH)D complex through megalin-mediated endocytosis.

Renal 1α-hydroxylase activity starts to decline even in the early stages of CKD will help to prevent progression of kidney disease and reduce the risk of CVD events. In recent years, vitamin D deficiency has been recognized as a prominent feature of CKD, and there is evidence to suggest that vitamin D deficiency in turn accelerates the progression of kidney disease. However, most of these studies were conducted in high-risk populations, and there are limited longitudinal studies evaluating this issue in general populations, especially in Asia.
stages of CKD. Furthermore, proteinuria leads to loss of DBP-25(OH)D in the urine and thus reduces the megalin-mediated uptake of 25(OH)D. In addition, in the recent years the discovery of the fibroblast growth factor-23 (FGF23) has significantly affected our understanding of vitamin D metabolism. FGF23 is a bone-derived hormone that regulates systemic phosphate homeostasis and vitamin D through a novel bone-kidney axis. FGF23 inhibits renal tubular reabsorption of phosphate through mechanisms independent of parathyroid hormone, as well as reduces circulating 1,25(OH)2D levels in the early phase of CKD. Furthermore, Faul et al demonstrated that excess FGF23 may directly induce left ventricular hypertrophy in rats. Therefore, vitamin D deficiency, particularly, 1,25(OH)2D deficiency, is commonly observed in patients with CKD even in the early stages of the disease. Increasing evidence has demonstrated a correlation between vitamin D deficiency and progression of CKD, and plasma vitamin D status is an independent inverse predictor of disease progression and death in patients with CKD. Thus, vitamin D deficiency may in fact accelerate the progression of kidney disease.

In this issue of the Journal, Izumaru et al report their retrospective analysis of a large CKD cohort to describe the relationship between serum 1,25(OH)2D levels and the development of CKD stages 3–5 in a general Japanese population. Their study demonstrated that lower serum 1,25(OH)2D levels were significantly associated with an increased risk of the development of CKD stages 3–5. However, no significant association between serum 1,25(OH)2D and the multivariable-adjusted odds ratio of albuminuria for 5 years was observed. These contrasting results between estimated GFR (eGFR) and albuminuria were unexpected, and therefore more longitudinal studies are needed. In a large cohort cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III), vitamin D insufficiency was found to be associated with increased prevalence of albuminuria, suggesting that vitamin D has an intrinsic anti-proteinuria effect.

**Molecular Mechanism Underlying the Renoprotective Action of Vitamin D**

The data from experimental and clinical studies published in recent years suggest that vitamin D and its analogs protect the kidney (Figure). The antiproteinuria effect of vitamin D and its analogs is crucially significant because proteinuria is a major risk factor for the progressive decline of renal function. Podocytes are critically important in overall glomerular function and structure. Injury to them commonly leads to proteinuria and glomerulosclerosis. Podocytes have a vitamin D receptor, which is markedly upregulatable, and the podocyte nucleus has a vitamin D response element in its DNA near the promoter start site for nephrin gene. Vitamin D stimulates nephrin mRNA and protein. Nephrin is an essential protein in the slit pore membrane of the glomerulus. Further, the RAS and NF-κB activation pathway have major roles in causing renal damage. They promote the production of proinflammatory and proinflammatory factors, increase oxidative stress, and damage podocytes. Angiotensin II (Ang II) also exerts hemodynamic effects on glomeruli to induce proteinuria. Ang II can activate NF-κB, which in turn stimulates angiotensinogen expression, forming a vicious circle. Vitamin D and its analogs inhibit renin expression and suppress NF-κB activation by disrupting its DNA binding. Vitamin D and its analogs also suppress angiotensinogen expression by targeting NF-κB, thus breaking the vicious circle.

Vitamin D and its analogs may directly induce left ventricular hypertrophy in rats. Furthermore, an activator of the NF-κB response element 2 (Nrf2)/Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 (Keap1) antioxidant pathway was reported to ameliorate kidney function in type 2 diabetes. Nakai et al reported that vitamin D analog inhibited the hyperglycemia-induced downregulation of Nrf2, suggesting that vitamin D therapy could attenuate the progression of diabetic nephropathy by amelioration of the Nrf2-Keap1 pathway and suppression of NF-κB and oxidative stress.

Growing evidence from a number of experimental models and clinical studies presents a very strong case for a renoprotective role for vitamin D and its analogs in the development of kidney disease. We need to understand whether amelioration of serum 1,25(OH)2D levels could result in improvements in CKD progression and CVD events.

**References**