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EDITORIAL

Editorial over the Many Faces of Vitamin D in Chronic Kidney Disease: from Mineral to Immune-Inflammatory Modulator

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Vitamin D (vit D), whether produced in the skin or absorbed from the diet, is first metabolized in the liver to generate 25-hydroxyvitamin D (25OHD) and then hydroxylated in the proximal renal tubule to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). $1,25(OH)_2D$ (calcitriol) is the major biologically active metabolite and serves a paracrine/autocrine function. $1,25(OH)_2D$ forms a complex with the vit D nuclear receptor which binds to vit D response elements in the deoxyribonucleic acid (DNA). Thousands of these binding sites regulate hundreds of genes creating a multitude of genomic effects that modulate cell activation, proliferation, and differentiation within the immune-inflammatory system [1]. This underpins the biological rationale for a potential beneficial partnership of vit D in a variety of immune-inflammatory conditions that largely transcends its undisputed regulatory role in calcium/phosphate homeostasis and bone mineralization [2, 3].

Chronic kidney disease (CKD) is an intricate pathology characterized by a state of accelerated cardiovascular deterioration. Persistent inflammation has been recognized as an important component of CKD and may in part account for cardiovascular and all-cause mortality [4]. Low levels of both 25OHD and $1,25(OH)_2D$ are observed in patients with CKD and are associated with higher mortality and faster progression of kidney disease [5]. In a recent issue of Inflammation, Zhao et al. showed that calcitriol significantly reduced tubulo-interstitial inflammation in a rodent renal injury model [6]. The authors linked this renoprotective effect to calcitriol-induced up-regulation of zinc finger protein A20, a de-ubiquitinating enzyme which causes disruption of nuclear factor kappa B (NF-κB) dependent intracellular chemo- and cytokine production and suppresses apoptotic pathways [7].

Whether this novel compelling insight into the cellular mechanism of action of vit D may change the current or future therapeutic approach of CKD is uncertain. Factors contributing to the progression of CKD are indeed not limited to perturbed mineral metabolism, chronic inflammation, and oxidative stress but also include protein-energy wasting, pre-existing heart failure, arterial hypertension, iron deficiency, and dialysis-related injury [8]. Patients with CKD often present a "leaky gut" and/or profound alterations in gut microbial flora. Increased gut wall permeability promotes translocation of bacteria and endotoxin which continuously fuels an inflammatory state. Changes in the intestinal microbiome are highly determined by intraluminal influx of urea, dietary constituents, and occasional antimicrobial therapy [8, 9]. Of note is that both intestinal leakage and microbial environment show large interpatient variability and cannot be quantified. In addition, accumulation of protein-bound toxins (*e.g.*, p-cresyl sulfate and indoxyl sulfate) [10] and altered mucosal defense mechanisms may also contribute to cardiovascular events and sustain inflammation.

Despite robust *in vitro* arguments to support the renoprotective potential of vit D supplementation in CKD, hard clinical outcome data are lacking. A meta-analysis of randomized controlled trials showed that treatment with paricalcitol, a selective activator of the vit D receptor promoting sequestration of NF-κB signaling [11], lowered the risk of cardiovascular events in CKD patients but failed to reduce proteinuria and to protect renal function [12]. Vit D therapy neither improved vascular endothelial function nor attenuated inflammation in patients with CKD treated either with cholecalciferol or calcitriol for 6 months [13]. Likely explanations of these negative outcomes are

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the use of different vit D dose regimens, attempted correlations with 25OHD instead of active hormone plasma levels, the effect of renal replacement therapy, and the possible impact of other pathophysiological pathways that are related with vit D. Among the latter, the renin-angiotensin-aldosterone system (RAAS) stands out as a crucial regulator of intravascular volume and blood pressure in CKD. Calcitriol modulates the RAAS system by suppressing renin gene and angiotensin-converting enzyme expression [14, 15]. Blocking RAAS with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers controls arterial hypertension, reduces proteinuria, and prevents or reverses endothelial dysfunction and atherosclerosis in patients with CKD [16]. Endothelin (ET)-1-induced signaling pathways in vascular smooth muscle cells represent another attractive target for improving cardiovascular morbidity in CKD. ET type A receptor blockade reduced vascular inflammation and smooth muscle cell differentiation in rats with CKD [17]. In experimental CKD models, the combination of RAAS inhibition with ET receptor antagonism ameliorated proteinuria, renal structural changes, and molecular markers of glomerulosclerosis, renal fibrosis, or inflammation more effectively than RAAS inhibitors or ET receptor antagonists alone [18].

Taken together, the findings of Zhao et al. confirm the immune-inflammatory modulating capacity of vit D and expand the molecular basis to further explore its therapeutic potential in CKD. However, whether unveiling the role of A20 in calcitriol's renoprotection will lead to more effective treatment remains to be proven.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The authors declare that they have no competing interests.

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