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# Therapeutic role and potential mechanisms of active Vitamin D in renal interstitial fibrosis

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**Abstract**

Vitamin D, especially its most active metabolite 1,25-dihydroxyvitamin $D_3$ or calcitriol, is essential in regulating a wide variety of biologic processes, such as calcium homeostasis, immune modulation, cell proliferation and differentiation. Clinical studies show that the circulating level of calcitriol is substantially reduced in patients with chronic renal insufficiency. Administration of active Vitamin D results in significant amelioration of renal dysfunction and fibrotic lesions in various experimental models of chronic kidney diseases. Active Vitamin D elicits its renal protective activity through multiple mechanisms, such as inhibiting renal inflammation, regulating renin–angiotensin system and blocking mesangial cell activation. Recent studies indicate that calcitriol induces anti-fibrotic hepatocyte growth factor expression, which in turn blocks the myofibroblastic activation and matrix production in interstitial fibroblasts. Furthermore, in vivo and in vitro studies demonstrate that active Vitamin D effectively blocks tubular epithelial to mesenchymal transition (EMT), a phenotypic conversion process that plays a central role in the evolution of renal interstitial fibrosis. Together, it is becoming increasingly clear that a high level of active Vitamin D may be obligatory in the maintenance of normal kidney structure and function. Thus, supplementation of active Vitamin D could be a rational strategy for the therapeutics of chronic kidney diseases.


*Keywords:* Vitamin D; Renal fibrosis; EMT; Chronic kidney disease; HGF; TGF-β

## 1. Introduction

Clinical studies have established that the circulating level of active metabolite of Vitamin D, 1,25-dihydroxyvitamin $D_3$ or calcitriol, is substantially reduced in patients with chronic renal insufficiency [1,2]. This perhaps is not surprising, considering that renal tubular epithelial cells are the active sites for the calcitriol synthesis and the uptake of its precursor. A reduced number of functional nephrons in chronic kidney disease (CKD) would, therefore, result in active Vitamin D deficiency. On the flipping side of the same token, deficiency in active Vitamin D may be a causative factor contributing to nephron loss and progression of CKD, in light of its role in the maintenance of normal kidney structure and function. In this context, supplementation of active Vitamin D might provide a rational strategy to break up the vicious cycle between active Vitamin D deficiency and progression of renal failure, thereby slowing the progression of kidney dysfunction and fibrotic lesions in CKD [3].

Experimental data are accumulating in support of a renoprotective role of active Vitamin D in various forms of CKD [4–6]. In diverse animal models as well as in clinical trials involving patients with chronic renal insufficiency, active Vitamin D has proven to be beneficial, resulting in substantial attenuation of renal fibrosis and kidney dysfunction. Although earlier studies are largely focused on primary glomerular diseases [5,7], recent investigations indicate that active Vitamin D is also effective in reducing renal interstitial fibrosis [6]. Meanwhile, studies in cultured kidney cells have provided significant insights into the mechanisms underlying the beneficial effect of active Vitamin D on diseased kidney. The aim of this article is to integrate the related information about application of active Vitamin D in animal models of CKD, and to discuss the recent advance in our understanding of the

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cellular and molecular pathways leading to its anti-fibrotic actions.

## 2. Therapeutic role of active Vitamin D in chronic kidney diseases

The therapeutic potential of active Vitamin D is extensively evaluated in rat remnant kidney after subtotal nephrectomy (SNX), a classic CKD model characterized by primary glomerular lesions. Several studies performed in this model consistently demonstrate that active Vitamin D is capable of reducing albuminuria and glomerulosclerosis [4,5,7]. In all studies, administration of active Vitamin D results in less glomerulosclerosis and reduced albuminuria, accompanied by a suppression of glomerular cell proliferation. By using the parathyroidectomized SNX rats, it is shown that the renal beneficial action of calcitriol was independent of its influence on parathyroid hormone (PTH) level [5]. Active Vitamin D also reduces serum creatinine in this model, suggesting that it is able to normalize renal function [7].

In rat anti-Thy-1 mesangial proliferative glomerulonephritis model, active Vitamin D administration prevents albuminuria, extracellular matrix (ECM) accumulation, inflammatory infiltration and apoptosis [8,9]. Moreover, it has been proposed that some effects of active Vitamin D might be mediated through TGF-β1 [8], the well-known pathogenic mediator that plays a crucial role in the onset and progression of various CKD [10–12].

The therapeutic effects of active Vitamin D appear to go beyond the glomeruli. We have recently evaluated the efficacy of active Vitamin D in mouse nephropathy induced by unilateral ureteral obstruction (UUO), a widely used, aggressive interstitial fibrosis model characterized by rapid tubular atrophy and interstitial expansion and matrix deposition. By using paricalcitol (19-nor-1,25-hydroxy-vitamin $D_2$), a synthetic, non-hypercalcemic Vitamin D analogue that has been approved in the treatment of secondary hyperparathyroidism in end-stage renal disease patients, we found that activation of Vitamin D receptor significantly reduced the fibrotic lesions in obstructed kidney in a dose-dependent fashion, as demonstrated by a reduced interstitial volume and decreased deposition of interstitial matrix components [6]. Paricalcitol substantially inhibited renal mRNA expression of fibronectin, types I and III collagen, and fibrogenic TGF-β1, while preserved E-cadherin and Vitamin D receptor (VDR) expression in the obstructed kidney [6]. These findings are consistent with the notion that active Vitamin D is also effective in preventing renal interstitial lesions.

The renal protective roles of active Vitamin D in animal models have inspired several clinical trials exploring its effectiveness in CKD patients. Recently, a randomized, double-blinded and placebo-controlled clinical trial has shown the renal protective effect of paricalcitol in the patients of end-stage renal diseases (ESRD), with an improved proteinuria [13]. In addition, epidemiologic studies also demonstrate that active Vitamin D prolongs the graft survival duration and lowers the rate of renal function loss in human kidney transplant recipients [14]. Therefore, data are emerging to suggest a renoprotective action of active Vitamin D in patients with chronic renal insufficiency.

## 3. Potential mechanisms underlying the beneficial effects of active Vitamin D

Active Vitamin D could elicit its renoprotective actions by targeting different types of kidney and immune cells via multiple mechanisms. Two actions of active Vitamin D may have systemic impact on the progression of CKD. One is its anti-inflammation potential [15]. Through the inhibition of inflammatory infiltration, active Vitamin D essentially diminishes many detrimental effects of glomerular and/or interstitial inflammation in response to various injuries. Another is the ability of active Vitamin D to inhibit renin gene expression. In a series of elegant studies, Li et al. demonstrate that renin gene is negatively controlled by Vitamin D receptor [16,17]. Thus, active Vitamin D and VDR are mechanistically linked to the renin–angiotensin system (RAS), which in turn plays a critical role in the regulation of renal hemodynamic adaptation and fibrogenic responses in CKD. Detailed discussion on these aspects, which can be found in several comprehensive reviews [17,18], is beyond the scope and intent of this article.

Active Vitamin D also exerts some cell-type-specific actions in different kidney cells. Earlier works on Vitamin D action in kidney are largely focused on glomerular mesangial cells, because their activation is believed to play a decisive role in the over-production and deposition of glomerular ECM components, leading to glomerulosclerosis as seen in many primary glomerular diseases. Active Vitamin D binds to VDR with high affinity in cultured human renal mesangial cells, which often results in an inhibition of mesangial cell proliferation [19]. It is generally believed that the anti-proliferative property of active Vitamin D in mesangial cells plays an essential role in mediating its beneficial actions.

Recent studies have identified podocytes as another target of active Vitamin D [4,20]. Podocyte possesses VDR, and administration of active Vitamin D markedly protects podocytes from injury in both immune and non-immune mesangial proliferative glomerulonephritis rat models. In SNX rat model, calcitriol effectively reduces podocyte hypertrophy, improves podocyte ultrastructure and suppresses the expression of desmin, a podocyte injury marker [4]. It is becoming obvious that the anti-proteinuria effect of active Vitamin D is closely related to, and perhaps dependent of, its ability to preserve the structural and functional integrity of podocytes.

The action of active Vitamin D in podocytes and mesangial cells principally accounts for its beneficial effects on proteinuria and glomerluosclerosis, the hallmarks of primary glomerular diseases. However, active Vitamin D is also