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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 D₃ 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 D₃ or calcitriol, is substantially reduced in patients with chronic renal insufficiency [1,2]. This 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

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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 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- β 1 [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 D₂), a synthetic, nonhypercalcemic 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, type I and type III collagen, and fibrogenic TGF- β 1, 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 and colleagues demonstrate that renin gene is negatively controlled by vitamin D receptor (VDR) [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 glomerulosclerosis, the hallmarks of primary glomerular diseases. However, active vitamin D is also able to attenuate renal tubulointerstitial fibrosis, the common final outcome of diverse types of CKD. Besides its systemic impacts on RAS and inflammation as discussed above, we recently found that active vitamin D inhibits myofibroblast activation from interstitial fibroblasts and blocks tubular EMT (see below), underscoring that it can directly target the central events in renal interstitial fibrogenesis.

4. Vitamin D receptor activation induces anti-fibrotic HGF expression

In view of its therapeutic effectiveness in renal interstitial fibrosis, we have sought to examine the direct effect of active vitamin D on myofibroblast activation, one of the key events that lead to matrix over-production and deposition. Renal myofibroblast, an activated fibroblast with expression of a molecular hallmark α -smooth muscle actin (α -SMA), is generally considered as the principal matrix-producing effector cells that are responsible for the excess production of ECM components in the fibrotic tissues. It turns out that calcitriol effectively blocks myofibroblast activation from interstitial fibroblasts, as evidenced by suppression of TGF- β 1-mediated α -SMA expression [21]. Meanwhile, active vitamin D also inhibits type I

collagen and thrombospondin-1 expression in cultured renal interstitial fibroblasts (NRK-49F) [21].

The inhibitory effect of active vitamin D on myofibroblast activation in many aspects imitates the action of hepatocyte growth factor (HGF), an anti-fibrotic factor that has been previously shown to inhibit myofibroblast activation [22,23]. Interestingly, there is vitamin D response element (VDRE) in the regulatory region of HGF gene [24]. These observations prompted us to test whether active vitamin D stimulates HGF expression. Indeed, calcitriol induces HGF mRNA expression and protein secretion in renal interstitial fibroblasts (Figure 1). Renal fibroblasts express VDR, which binds to the VDRE in the HGF promoter region and *trans*-activates HGF promoter in a ligand-dependent fashion. Furthermore, calcitriol is able to stimulate HGF receptor tyrosine phosphorylation in renal fibroblasts, and HGF-neutralizing antibody largely abolishes calcitriol-mediated suppression of myofibroblast activation [21]. Hence, a linkage between active vitamin D and anti-fibrotic HGF is established, which may provide a mechanistic insight into understanding how active vitamin D inhibits myofibroblast activation.

Because HGF is a secreted protein and its receptor is ubiquitously expressed, this suggests, at least in theory, that active vitamin D may have broad effects on many types of kidney cells, by virtue of its induction of HGF expression. In that regard, the anti-fibrotic effect of active vitamin D may not be limited to renal interstitial fibroblasts, but could be extended to other kidney cells as well in vivo. As depicted in Figure 1C, HGF has been shown to inhibit mesangial cell activation and matrix production, primarily by upregulating Smad corepressor TGIF expression via blocking its degradation [25]. In interstitial fibroblasts, HGF prevents activated Smad2/3 from nuclear translocation, thereby blocking the access of activated Smad2/3 to the regulatory region of the target genes [22]. In tubular epithelial cells, HGF induces another Smad corepressor SnoN gene expression, which in turn binds to activated Smad2/3 and sequesters their *trans*-activating ability [26,27]. In short, HGF signaling is capable of intercepting TGF- β 1/Smad signaling in different types of kidney cells by diverse mechanisms (Figure 1C). It is conceivable that the anti-fibrotic actions of HGF could be shared by active vitamin D, considering its ability to induce HGF expression. However, there is a note of caution. HGF induction apparently requires a high concentration of active vitamin D (Figure 1B). It remains to be determined whether that level of active vitamin D is achievable in vivo.

5. Active vitamin D targets tubular epithelial to mesenchymal transition

In vivo studies show that active vitamin D preserves the integrity of tubular epithelium by restoring E-cadherin and VDR expression in obstructive nephropathy [6], consistent with its pro-differentiation potential. In the fibrotic kidney after sustained injury, tubular epithelial cells undergo a phenotypic transition known as EMT to become myofibroblasts [28,29]. The pathologic impact of tubular EMT on renal fibrogenesis is two folds: it leads to tubular atrophy due to a decreased epithelial cell mass, and it increases the matrix-producing effector cells. Emerging evidence suggests that EMT is a crucial event in the evolution of renal interstitial fibrosis; accordingly, blockade of EMT process via various strategies ameliorates fibrotic lesions in vivo [26,30]. We have recently found that active vitamin D directly block tubular EMT induced by TGF- β 1 in cultured tubular epithelial cells, as demonstrated by restoring E-cadherin expression and suppressing α -SMA and fibronectin expression. Therefore, active vitamin D can target a key cellular event in renal interstitial fibrogenesis.

Although tubular EMT is very complex, the entire EMT course at cellular level is consisted of four key steps, in which loss of epithelial cell-cell adhesion property, as manifested by suppression of E-cadherin, is an early, initial event [28,31]. Our recent studies demonstrate that active vitamin D preserves E-cadherin expression by suppressing Snail and Id expression

(Figure 2). In normal physiologic conditions, E-proteins, a family of basic helix-loop-helix (bHLH) transcription factors, form a homo- or heterodimers and bind to the E-boxes in the E-cadherin promoter and *trans*-activate its gene transcription. However, in the fibrotic kidney or upon stimulation with TGF- β 1 in vitro, tubular epithelial cells over-express Snail and Id proteins. Snail, a zinc-finger transcription factor that plays a critical role in EMT in a wide range of carcinomas [32–34], possesses DNA-binding capacity and is able to specifically bind to the core E-box, thereby displacing E-proteins and sequestering their ability to activate E-cadherin gene expression (Figure 2). Id, a family of transcriptional inhibitors, represents a truncated form of bHLH proteins. Because of lacking the basic DNA-binding region, Id is unable to bind to DNA but retains its ability to heterodimerize with other E-proteins, and thus functions as a transcriptional antagonist in a dominant-negative fashion [35]. Increased Id, therefore, physically binds to E-proteins and prevents their interacting with E-box, thereby inhibiting the *trans*-activating capacity of E-proteins (Figure 2). The ability of active vitamin D to inhibit both Snail and Id in vivo and in vitro highlights that it can restore E-cadherin and preserve the integrity of tubular epithelium in CKD.

VDR gene harbors E-boxes and is therefore suppressed by Snail and Id in diseased kidney [36]. Through the similar mechanisms as described in Figure 2, active vitamin D effectively restores VDR expression in CKD. Studies also indicate that VDR could physically form complexes with β -catenin [37], a major signaling mediator that integrates the signals from diverse pathways and plays a critical role in EMT. β -catenin is known to form a complex with T cell transcription factor (TCF)-4; and together they *trans*-activate the transcription of their target genes. Ligand-activated VDR competes with TCF-4 for β -catenin binding, and represses β -catenin/TCF-4-mediated gene transcription. In this regard, down-regulation of VDR in CKD, in essence, removes the negative control mechanism for β -catenin signaling, and effectively promotes the expression of the EMT-related genes. Active vitamin D, through induction of VDR, restates the mechanism that confines β -catenin signaling, thereby preserving the tubular epithelial phenotypes of renal parenchyma.

At present, although the data regarding the role of active vitamin D in renal tubules are limited, available results have suggested a fundamental role for active vitamin D in the maintenance of the structural and functional integrity of tubular epithelium. As the pathologic significance of tubular EMT in renal fibrosis is increasingly recognized, so does the role of active vitamin D in renal protection.

6. Conclusion

Data from in vivo and in vitro experiments as well as clinical trials are emerging to suggest that active vitamin D and/or its analogous are renoprotective, resulting in an attenuation of glomerulosclerosis and interstitial fibrosis and an improvement of kidney functions. Dependent on the nature and etiologies of the CKD models, diverse actions of active vitamin D may account for its beneficial effects in vivo, which include the regulation of RAS system, anti-inflammation, podocyte protection, HGF induction and preservation of tubular epithelium via blocking EMT. Pharmacologic supplementation of active vitamin D may be a rational strategy to halt the vicious cycle between its deficiency and decline in kidney function in CKD patients. In this regard, active vitamin D may hold promise as a new addition to our anti-fibrotic armamentarium.

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Figure 1.

Active vitamin D may inhibit the activation of renal fibrogenic cells by inducing anti-fibrotic HGF expression. (A, B) Active vitamin D induces HGF mRNA expression and protein secretion in renal interstitial fibroblasts (NRK-49F), as shown by RT-PCR (A) and Western blot analyses (B). (C) Diagram shows the potential pathways leading to vitamin D inhibition of renal fibrosis. Ligand-bound VDR trans-activate HGF gene expression (1). Increased HGF upregulates Smad co-repressor TGIF expression and inhibits mesangial cell activation (2). HGF blocks the nuclear translocation of the activated-Smads in renal interstitial fibroblasts, thereby preventing myofibroblast activation (3). In tubular epithelial cells, HGF induces SnoN expression, thereby inhibiting TGF-β/Smad-mediated tubular EMT (4). TGF-β1, via its Smad signaling, promotes tubular EMT and myofibroblastic activation from glomerular mesangial cells and interstitial fibroblasts, respectively (5). Panels A and B of this figure are reproduced from the published work with permission [21].

Figure 2.

Active vitamin D preserves renal epithelial cell phenotypes by suppressing Snail and Id expression. In normal physiologic conditions, E-proteins, a family of bHLH transcription factors, bind to the E-boxes and *trans*-activate E-cadherin and vitamin D receptor genes (1). In the fibrotic kidney, an increased Snail and Id proteins repress E-box-mediated gene expression through distinctive mechanisms. Snail displaces E-proteins from binding to the E-boxes via its DNA-binding capacity (2), whereas Id sequesters the gene activating activity of E-proteins through physically interacting with them (3).