Vitamin D and Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is an emerging public health problem and one of the most powerful predictors of premature cardiovascular disease. Emerging evidence suggests that the progression of CKD and many of the cardiovascular complications may be linked to hypovitaminosis D. Patients with CKD have an exceptionally high rate of severe vitamin D deficiency that is further exacerbated by the reduced ability to convert 25-(OH)vitamin D into the active form, 1,25 dihydroxy-vitamin D. As new evidence has improved our understanding of classical, as well as the non-classical, functions for vitamin D, it has become apparent that the autocrine role of vitamin D is an important modulator of several systems including the immune, renal and cardiovascular systems. In addition to the traditional supplementation of 1,25-vitamin D to CKD patients, by assessing and repleting 25-(OH) vitamin D deficiency, physicians will adequately fuel both the renal and extra-renal pathways of calcitriol synthesis maintaining the classical, as well as the non-classical, functions of vitamin D that ultimately influence clinical outcomes in this high-risk group of patients. Because of the high rates of hypovitaminosis D and progression of CKD to end-stage renal disease in minority populations, these findings are highly relevant to the national efforts to reduce health disparities. Healthcare providers are called to join the intensified efforts of public health officials to disseminate and implement updated guidelines and recommendations to halt the growing epidemic of vitamin D deficiency, particularly in high-risk populations.

Keywords
Vitamin D; Chronic Kidney Disease; Cardiovascular

Introduction

In the past decade, an abundance of evidence has detailed a more expanded array of actions involving numerous regulatory processes for vitamin D in the body. The relevance of this is underscored by the parallel realization of the epidemic of hypovitaminosis D in the general population and by the already-established disproportionately high incidence of hypovitaminosis D in patients with chronic kidney disease (CKD). New evidence has now established that the role of vitamin D is no longer solely restricted to its classical function of maintaining calcium and phosphate homeostasis. Vitamin D appears to play a more extensive role as a cell differentiating and antiproliferative factor with actions in a variety of tissues, including the renal, cardiovascular, and immune systems. In patients with...
CKD, the new non-classical role of vitamin D also encompasses regulation of the renin-angiotensin system (RAS)\(^3,5\) and the nuclear factor (NF) \(\kappa B\) pathway,\(^2\) two pathways involved in a broad range of pathological processes.\(^3\) These emerging findings establish a new paradigm in approaching treatment to address both the classical and non-classical effects of vitamin D in patients affected by vitamin D deficiency, particularly those with CKD. It appears that adequate replacement of vitamin D in deficient populations could potentially reduce premature morbidity and mortality.\(^3,5\) These new data present convincing evidence for the necessity of administration of vitamin D both in the 25 and 1,25 forms to supplement both the classical endocrine renal 1-alpha-hydroxylase vitamin D pathway as well as the autocrine intracellular 1-alpha-hydroxylase pathway through which vitamin D has now been shown to function.\(^1\) The implications of these new data will serve to shift the approach to vitamin D replacement in CKD patients into a new era where use of vitamin D is no longer solely for the treatment of secondary hyperparathyroidism.\(^1,6\)

**Vitamin D**

Vitamin D is a prehormone obtained through the diet or via skin synthesis. It is subsequently activated in a sequential 2-step process, involving first 25-hydroxylation in the liver to produce 25-(OH)\(_2\)vitamin D and then 1-hydroxylation, which until recently was thought to occur primarily in the kidney, to produce the active product 1,25 vitamin D or calcitriol.\(^2,4,7\) The traditional dogma was that the 1,25 renal-activated end-product was responsible for all of the effects of the active vitamin D hormone in the body and that these effects were restricted to regulation of bone and mineral metabolism.\(^1,2\)

A more expanded role for 25-(OH)\(_2\)vitamin D was suggested by the ubiquitous existence of the vitamin D receptor in the body,\(^5,7,10\) the presence of at least 800 human genes for which there is a vitamin D response element,\(^2,7\) and the wide distribution of the 1-alpha-hydroxylase in non-renal tissues such as the skin, vascular smooth muscle cells, pancreas, kidney, heart, immune system, intestine and sarcoid tissue.\(^2,4\) In addition, it has been noted that the incidence of certain chronic non-osseous diseases, such as cancers and chronic infections, were strongly correlated with latitude and therefore lower cutaneous synthesis of vitamin D.\(^2,7\)

**Non-classical Role of Vitamin D**

Evidence now shows that, in addition to the classical pathway for activation of 25-(OH)\(_2\)vitamin D to 1,25-(OH)\(_2\)vitamin D, a peripheral autocrine pathway exists and results in calcitriol synthesis in a variety of peripheral (non-renal) tissues.\(^1,2\) In fact, it appears that the bulk of daily metabolic utilization of 25-(OH)\(_2\)vitamin D is via the peripheral autocrine pathway, although its contribution to circulating 1,25-(OH)\(_2\)vitamin D is minimal due to immediate local degradation.\(^2\) Calcitriol synthesized in this manner in the cells and tissues that possess these pathways serves as a critical component in the signaling cascades that bridge external stimuli to gene transcription.\(^1,2\) By binding with its intracellular vitamin D receptor (VDR) in these tissues, calcitriol can regulate cellular proliferation and differentiation, inflammation, the immune system and the endocrine system, including RAS, insulin resistance and lipid metabolism.\(^1,10\)

The discovery of this non-classical pathway (which is also present in renal tissue) has brought new significance to the importance of addressing nutritional vitamin D deficiency given the potential role that hypovitaminosis D may play in multiple chronic diseases such as diabetes, chronic infectious processes, hypertension, cardiovascular disease and CKD.\(^1,5\) Vitamin D deficiency is of high prevalence in the general population\(^5,7\) and patients with CKD are affected to an even greater degree.\(^1,5,6\)
**Non-classical Role of Vitamin D in CKD**

The kidney appears to be a major target organ for both the classical and non-classical actions of vitamin D, with the vitamin D receptor being appropriately highly expressed in this site.\(^3\) The non-classical effects of vitamin D may play a relevant role in the mortality and morbidity of patients with CKD, specifically affecting the possible progression of their renal disease\(^3\) and coexisting cardiovascular disease, which is the major cause of death in this population.\(^5\) (Figure 1)

One specific pathway that appears to be regulated by the autocrine function of vitamin D in the CKD patient is the renin-angiotensin system (RAS).\(^3\) This cascade features a sequential activation of angiotensin II, which, in patients with CKD, is likely to have deleterious effects on blood pressure and the vasculature, and may contribute to renal parenchymal damage.\(^3\) VDR (vitamin D receptor)-null mice have an increased expression of renin and angiotensin II production, which leads to hypertension, cardiac hypertrophy and increased water intake.\(^11\) However, with intact VDR activity, evidence suggests that these deleterious effects may be reversed through modulation of the RAS system and instead a beneficial effect on blood pressure, as well as on dysregulated vascular and cardiac function, may be found.\(^11\) Further, when activated vitamin D analogs are administered in animal models that mimic various stages of CKD, a suppressed activation of the RAS system was demonstrated along with concurrent attenuation of glomerular and tubulointerstitial destruction and improvement in blood pressure, underscoring the significance of this cascade in renal damage.\(^3,11\)

Another important role of the RAS appears to be in diabetic nephropathy, which remains one of the leading causes of CKD.\(^3\) Both hyperglycemia and vitamin D deficiency appear to be strong activators of the intra-renal components of the RAS. Indeed, research has shown that in diabetes, the intrarenal interstitial angiotensin II levels can reach as much as 1000 times higher than normal.\(^12\) In experimental diabetic models, use of vitamin D analogues to prevent RAS activation appears to have therapeutic benefit by augmenting the traditional inhibitors of RAS currently in use.\(^13\)

One of the hallmarks of nephropathy is albuminuria. Evidence from clinical studies\(^14\) and association data from the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated an inverse relationship between the level of vitamin D and degree of albuminuria.\(^15\) These findings suggest that vitamin D may have anti-proteinuric effects, likely via a RAS-angiotensin II-mediated mechanism.\(^3\)

In addition to its role in progression of renal disease and proteinuria, the locally synthesized intrarenal (autocrine) angiotensin II has an effect on the cardiovascular system by its effect on blood pressure, vascular smooth muscle cells and cardiac myocytes.\(^16\) Because cardiovascular disease is the major cause of death in CKD patients, the potential role of vitamin D repletion to positively regulate this system may be quite significant in affecting premature mortality associated with CKD.\(^5\)

Another pathway significant in CKD, which may be regulated by the non-classical autocrine actions of vitamin D is the NF-κB pathway.\(^3,17\) NF-κB refers to a group of transcription factors that modulate genes involved in the immune response as well as in the process of inflammation and fibrosis, which underlie the pathogenesis of CKD.\(^3\) In CKD patients, it appears that NF-κB may play a role in both the progression of renal disease and in diabetic nephropathy.\(^3\) Activation of the NF-κB pathway triggers a cascade of events yielding cytokines, chemokines and other inflammatory factors, which exacerbate tissue injury in the renal disease process.\(^3\) In diabetic nephropathy, angiotensin II appears to activate NF-κB, which in turn activates angiotensinogen expression in renal cells when hyperglycemia is present.\(^17\) This cycle is likely partly responsible for the local accumulation of angiotensin II in diabetic nephropathy.\(^3,17\)
Vitamin D has been shown in numerous studies to inhibit the activation of NF-κB and further studies have shown an inverse relationship between serum vitamin D levels and the degree of tissue inflammation present in various types of kidney disease.\textsuperscript{3,17}

**Treatment**

Given its new expanded role, the treatment paradigm for vitamin D supplementation in CKD has now shifted to assure that both the classical and non-classical requirements are met. As CKD progresses and renal mass decreases,\textsuperscript{4} the ability to produce renal hydroxylated 1,25 vitamin D diminishes and 1,25 vitamin D deficiency ensues.\textsuperscript{1,4} It is therefore necessary to replete 1,25 vitamin D using calcitriol or its analogues to compensate for the compromised production of 1,25 vitamin D, which occurs in the later stages of CKD (beyond Stage 3) so that the classical functions of hormonal 1,25 vitamin D may be addressed.\textsuperscript{1,4}

In contrast to its classical endocrine function, it appears that in CKD the autocrine function of vitamin D remains intact as long as 25-(OH) vitamin D, the necessary substrate, is available.\textsuperscript{1} No data exist demonstrating the loss of extra-renal-1-alpha-hydroxylase activity in any stage of CKD,\textsuperscript{1} and, in fact, it appears that this enzyme activity is maintained even in anephric patients.\textsuperscript{1} Although the mechanisms of these autocrine extra-renal pathways remain unaffected by renal dysfunction, patients with CKD are disproportionately deficient in the necessary substrate, 25-(OH) vitamin D, beginning in the very early stages of their disease.\textsuperscript{1,4,5} The reason for this marked 25-(OH) vitamin D deficiency even in early CKD is likely multifactorial and due in part to nutritional deficiency\textsuperscript{2} as well as superimposed increased renal loss of vitamin D binding protein, which occurs as a result of proteinuria, a common occurrence in CKD patients.\textsuperscript{1,6} Given the potential importance of these autocrine functions and their effects on the comorbidities, such as cardiovascular disease found in association with CKD,\textsuperscript{5} it is imperative that adequate amounts of vitamin D or 25-(OH) vitamin D be provided to support the production of autocrine-derived calcitriol.\textsuperscript{1}

In all patients, serum levels of 25-(OH) vitamin D are the prime indicator of the adequacy of substrate present to fuel the autocrine pathways, and these levels may also predict risk of CVD and mortality in CKD.\textsuperscript{5,16} All patients, including CKD patients, are considered to have suboptimal levels of vitamin D when serum values fall below 30–32 ng/mL\textsuperscript{7} and several recent reports suggest optimal serum levels of 25-(OH) vitamin D should be between 40 to 80 ng/mL.\textsuperscript{1,2}

Since vitamin D does not occur naturally in most foods,\textsuperscript{2,7} and since precautions to curtail sun exposure prevail, use of vitamin D supplements is now almost universally required.\textsuperscript{2,7} Supplementation may be safely achieved with the use of vitamin D\textsubscript{3} or vitamin D\textsubscript{2} in oral form. Vitamin D\textsubscript{3} or cholecalciferol is the natural form of the vitamin and the form synthesized in the skin during sun exposure.\textsuperscript{1,2,7} Vitamin D\textsubscript{2}, ergocalciferol, is a synthetic product made through a process of irradiating fungi.\textsuperscript{6,7} Increasing, though inconsistent, evidence suggests that vitamin D\textsubscript{3} is the superior form of the vitamin and may have some advantages over vitamin D\textsubscript{2}, namely increased potency as well as a reported decreased rate of metabolic degradation.\textsuperscript{2}

In CKD, supplementation with 25-(OH)-vitamin D is recommended at the inception of the disease, with the addition of calcitriol replacement beginning in Stage 3.\textsuperscript{1} Previously published recommendations for 25-(OH) vitamin D supplementation apparently had significantly underestimated the daily metabolic requirements of this vitamin.\textsuperscript{1} New data focused on the non-classical effects of vitamin D have now been translated into revised recommendations for the daily intakes in both normal subjects and those with CKD.\textsuperscript{1} Recent quantitative studies now suggest that doses as high as 4,000 international units (IU) daily may be required to maintain optimum levels of vitamin D in normal populations,\textsuperscript{1,2,7} and it is extrapolated that higher doses may be required in CKD patients to overcome the more profound deficits to which
they are prone. To achieve adequate repletion, one common estimation is that for each 100 IU of vitamin D administered, the serum level of 25-(OH) vitamin D will rise by 1 ng/mL, although there is wide individual variation in the response to vitamin D dosing. Toxicity does not appear to be a significant problem with vitamin D administration because of a wide margin of safety between doses recommended for repletion and doses considered unsafe.

**Conclusion**

Vitamin D has emerged as a vital compound in CKD with newly ascribed autocrine functions vastly different from its classical function in mineral homeostasis. To ignore the significance of this vitamin and its potential impact on morbidity and mortality in the CKD patient is no longer appropriate. In addition to the traditional supplementation of 1,25-vitamin D to CKD patients, by assessing and repleting 25(OH) vitamin D deficiency, physicians will adequately fuel both the renal and extra-renal pathways of calcitriol synthesis, maintaining the classical and non-classical functions of vitamin D that ultimately influence clinical outcomes in this high-risk group of patients. Because of the high rates of hypovitaminosis D and progression of CKD to end-stage renal disease in minority populations, this approach is highly relevant to national efforts to reduce health disparities. Primary care physicians are called to join the intensified efforts of nephrologists, endocrinologists, nutritionists, other specialists and public health agencies to disseminate and implement updated guidelines and recommendations to halt the growing epidemic of vitamin D deficiency, particularly in the highly susceptible CKD population. The results of emerging studies may herald novel agents, which may further modulate these vitamin D-related cell signaling pathways and contribute to many of the co-morbidities encountered in the CKD patient deficient in vitamin D.

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**References**


Fig 1.
Conceptual model of major pathways through which vitamin D deficiency in patients with chronic kidney disease (CKD) may lead to CKD progression and complications such as premature cardiovascular disease (CVD). VSM – vascular smooth muscle. Adapted from ref 17.